Hepatitis A and Hepatitis C Viruses
A Clinical Overview

Marc G. Ghany, MD, MHSc

Liver Diseases Branch, NIDDK

Blood Moon

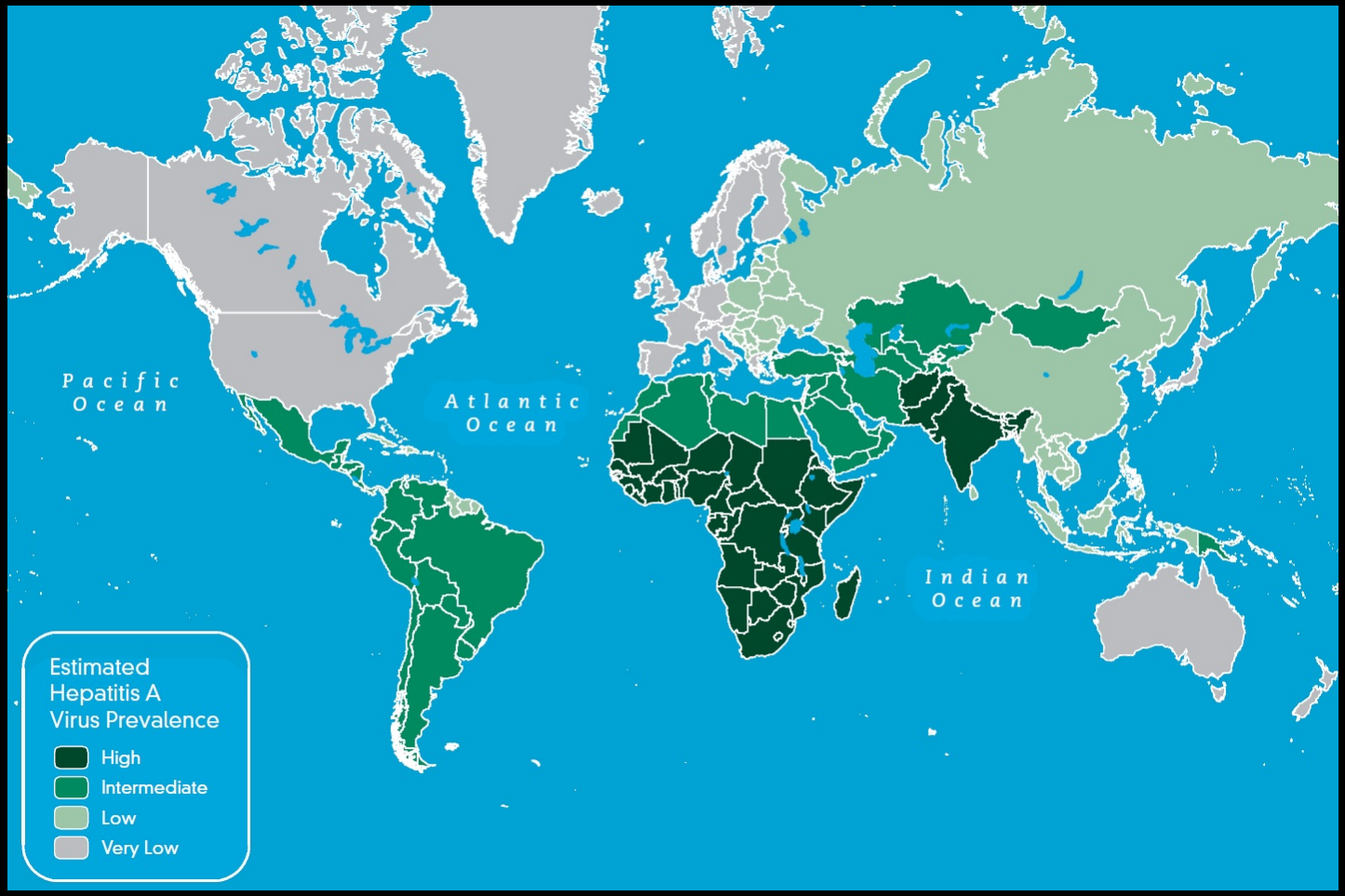
Overview of Hepatitis A and Hepatitis C Viruses

Characteristic	Hepatitis A virus	Hepatitis C virus
Source	Stool	Blood
Transmission	Enteric	Percutaneous/ Permucosal
Acute hepatitis	Yes	Yes
Acute infections ($x10^5$ persons/year), USA	0.4	0.3
Fulminant hepatitis	Yes	Yes
Fulminant deaths/year, US	100	?
Risk for chronic hepatitis and hepatocellular carcinoma	No	Yes
Available therapy	No	Yes
Available vaccine	Yes	No

Hepatitis A Virus: Overview

- Has existed for centuries
- One of the most common causes of infectious jaundice worldwide
- Usually associated with self-limiting hepatitis
- ~1,500,000 cases annually worldwide
- 1,398 reported cases of acute HAV in the U.S. in 2011
- Estimated cases ~2,800 in 2011
- Etiological agent of ~50% of all reported cases of acute viral hepatitis in the U.S

Hepatitis A: Global Prevalence

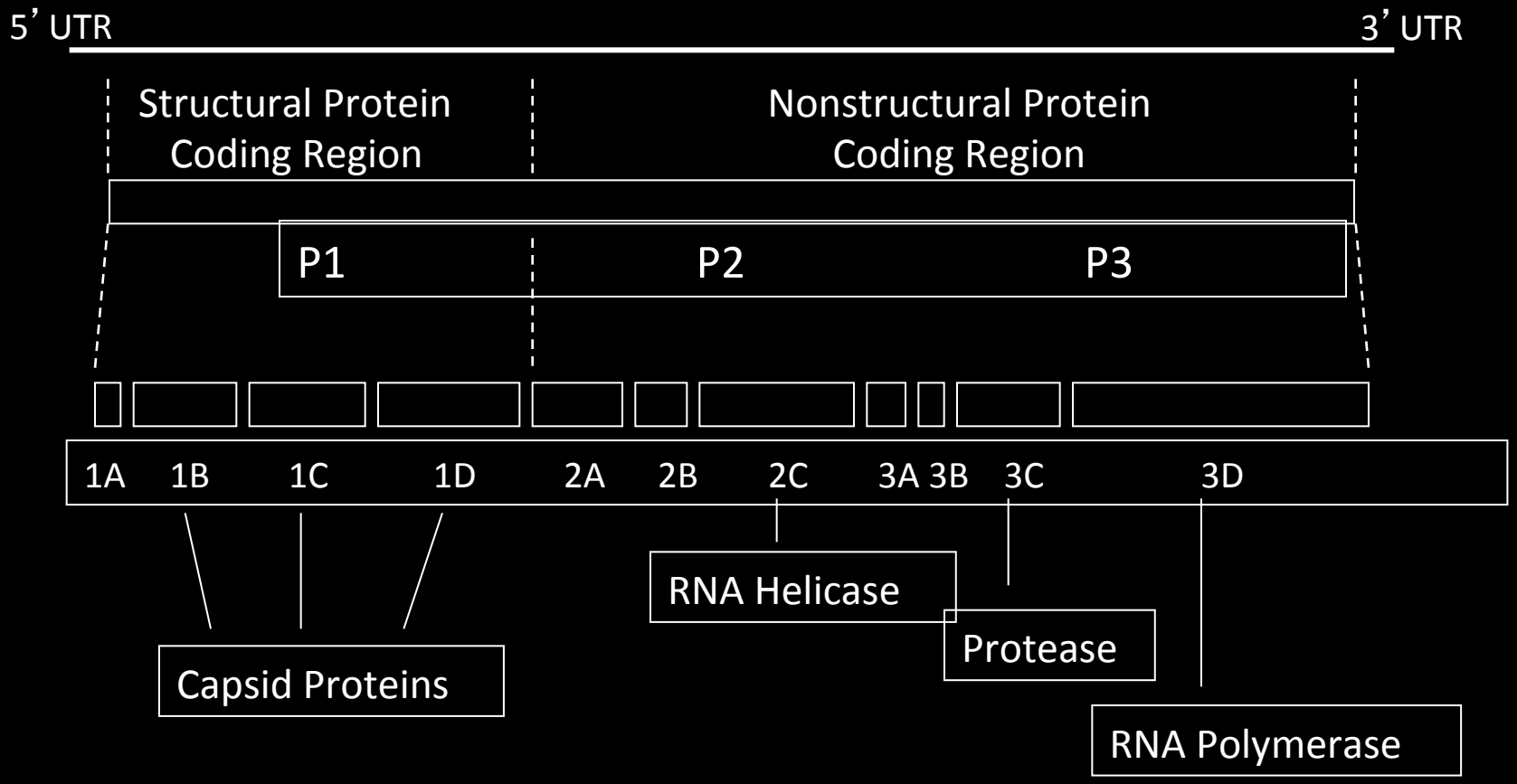


Jacobsen KH et al. *Vaccine* 2010;**28**:6653-6657

Hepatitis A: Epidemiology

- Highly endemic regions: most infections occur in children
- Intermediate areas of endemicity areas: most infections occur in adolescents and adults
- Low and very low areas of endemicity: most infections occur in adolescents and adults at high risk (IDU and travelers) and during outbreaks

Hepatitis A virus
Genomic Organization



Hepatitis A: Genotypes and Serotypes

- 4 genotypes affect humans (I, II, III & VII)
- Only one serotype

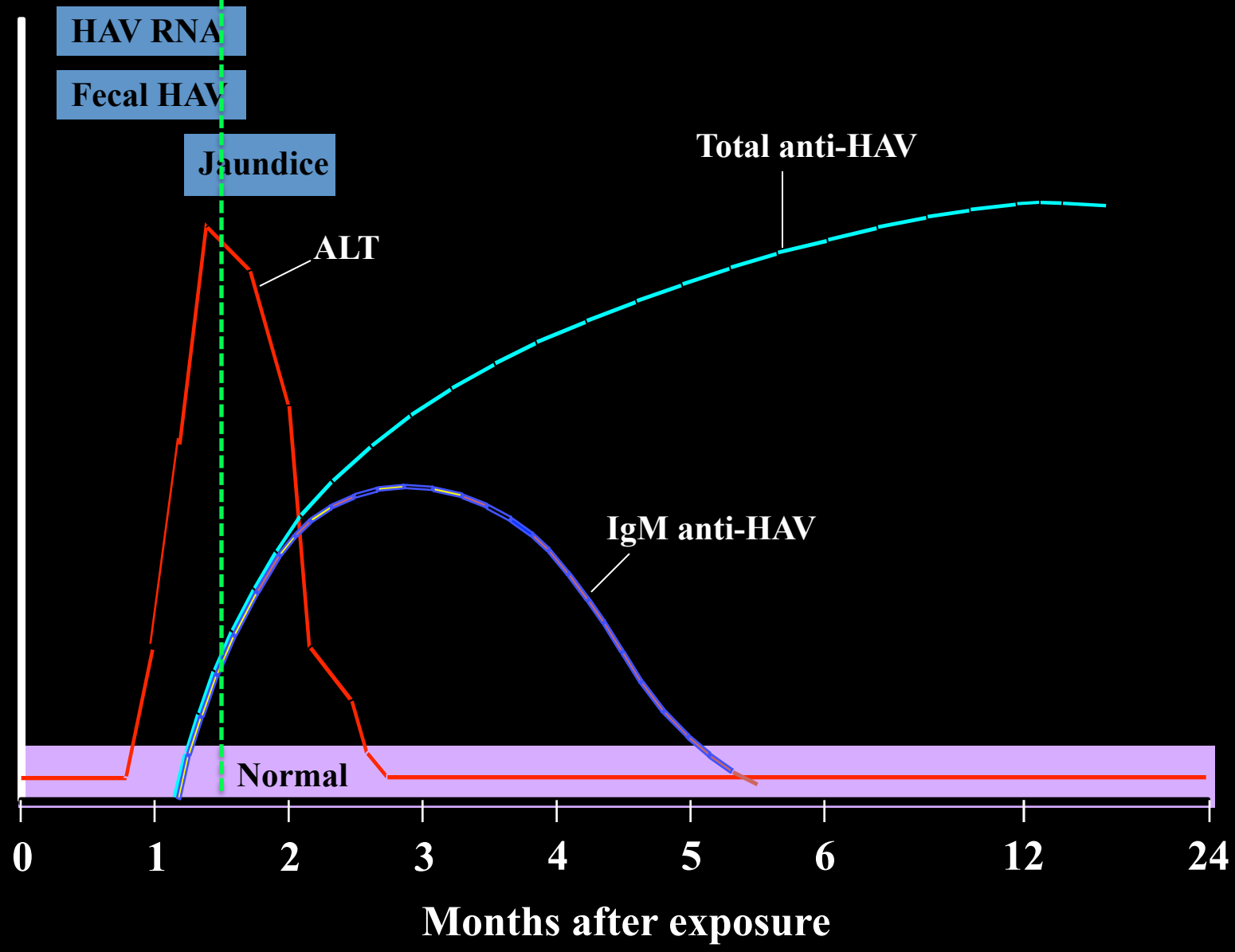
Hepatitis A: Transmission

- Fecal-oral route (Most common)
  - Person-person spread
  - Intrafamilial
  - Intrainstitutional
- Percutaneous (rare)
- Sexual (rare)

Hepatitis A: Clinical Features

- Incubation period averages 28 days (range, 15–50 days)
- Clinical manifestations include fever, malaise, anorexia, nausea, and abdominal discomfort, followed within a few days by jaundice.
- Severity of illness increases with age

Hepatitis A: Clinical Course



Hepatitis A: 5 Clinical Patterns

- Asymptomatic
- Symptomatic with jaundice self-limited to <8 weeks
- Cholestatic with prolonged duration of jaundice >10 weeks
- Relapsing, consisting of two or more bouts of acute HAV infection occurring over a 6-10 week period (10% of cases)
- Fulminant hepatitis (1-5% of cases)

Hepatitis A: Outcome

- Recovery is the rule
- Chronic infection does not occur

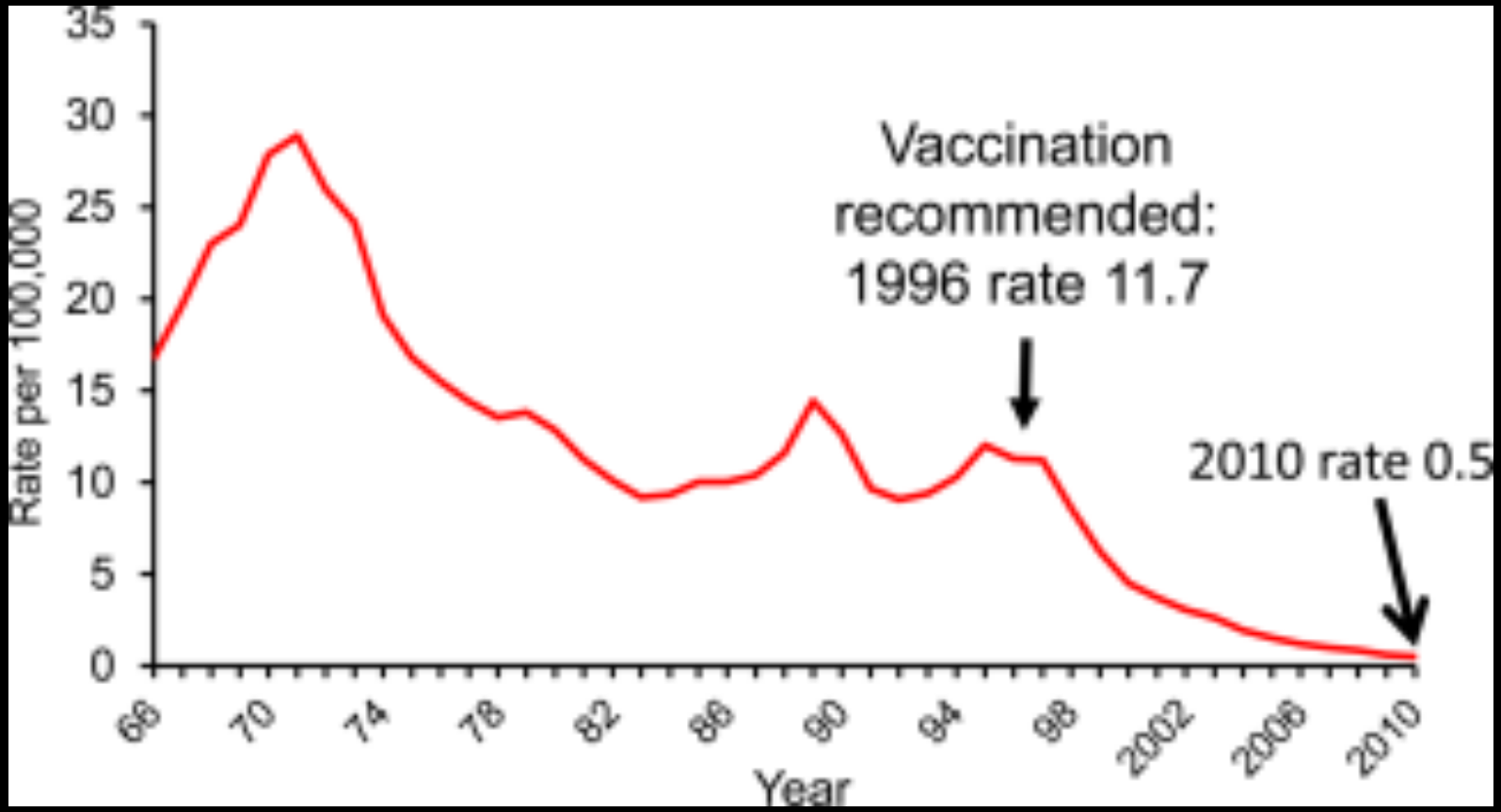
Hepatitis A: Treatment

- None Required
- Supportive Care

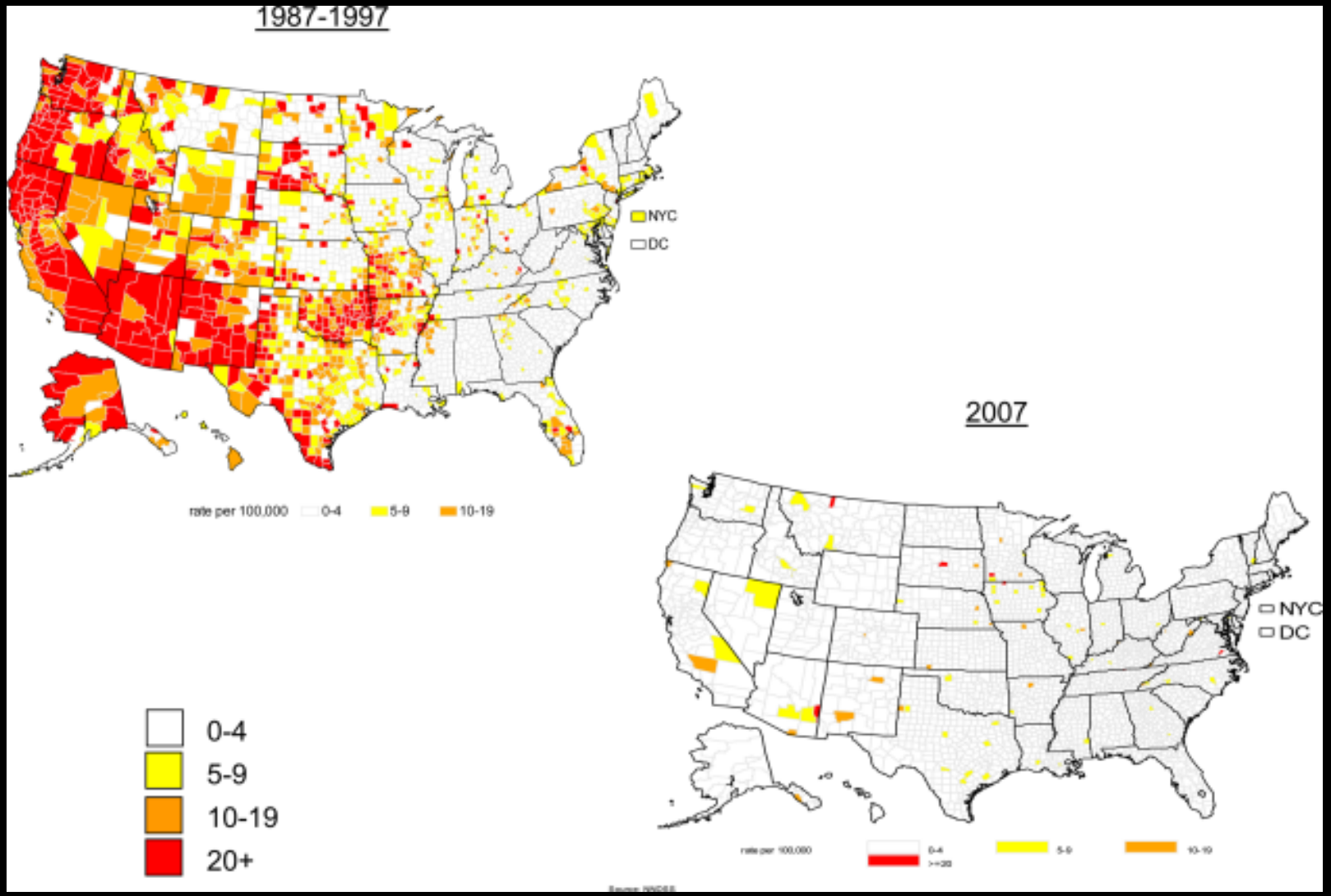
Hepatitis A: Prevention

- Serum immunoglobulin
- Vaccines
  - Havrix
  - Vaqta

Hepatitis A: Declining Incidence in the U.S Following Mandatory Vaccination



Hepatitis A: Declining Incidence by County in the U.S.



Hepatitis A: Who Should Be Vaccinated

- Children between ages of 2 and 18 years in existing programs
- International travelers
- Persons who anticipate close contact with an international adoptee
- Men who have sex with men
- Illicit drug users
- Persons with chronic liver disease
- Persons receiving clotting factor concentrates
- Persons who work with HAV-infected primates or with HAV in research settings
- Anyone who wants to obtain immunity

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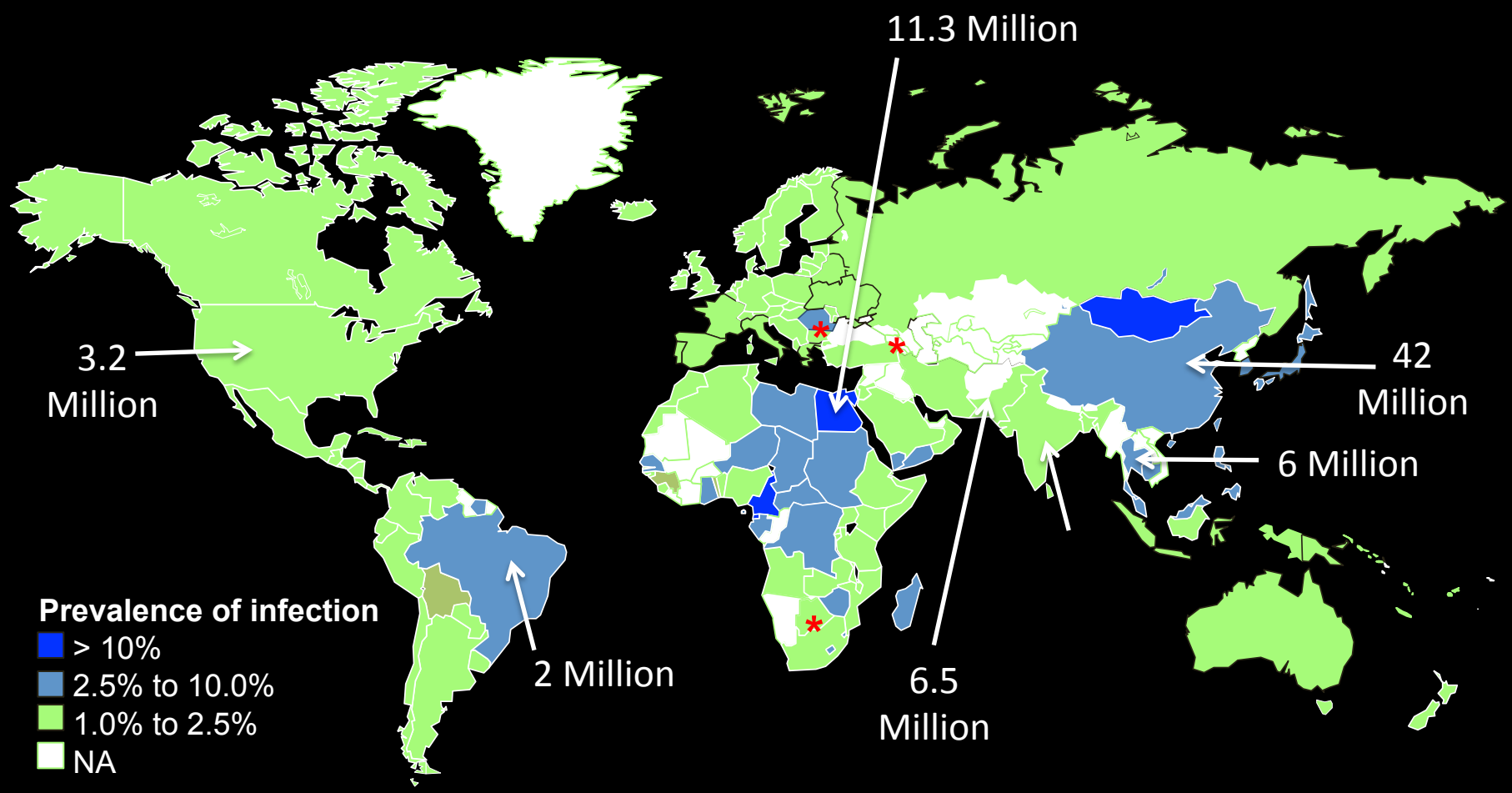
Chronic Hepatitis C

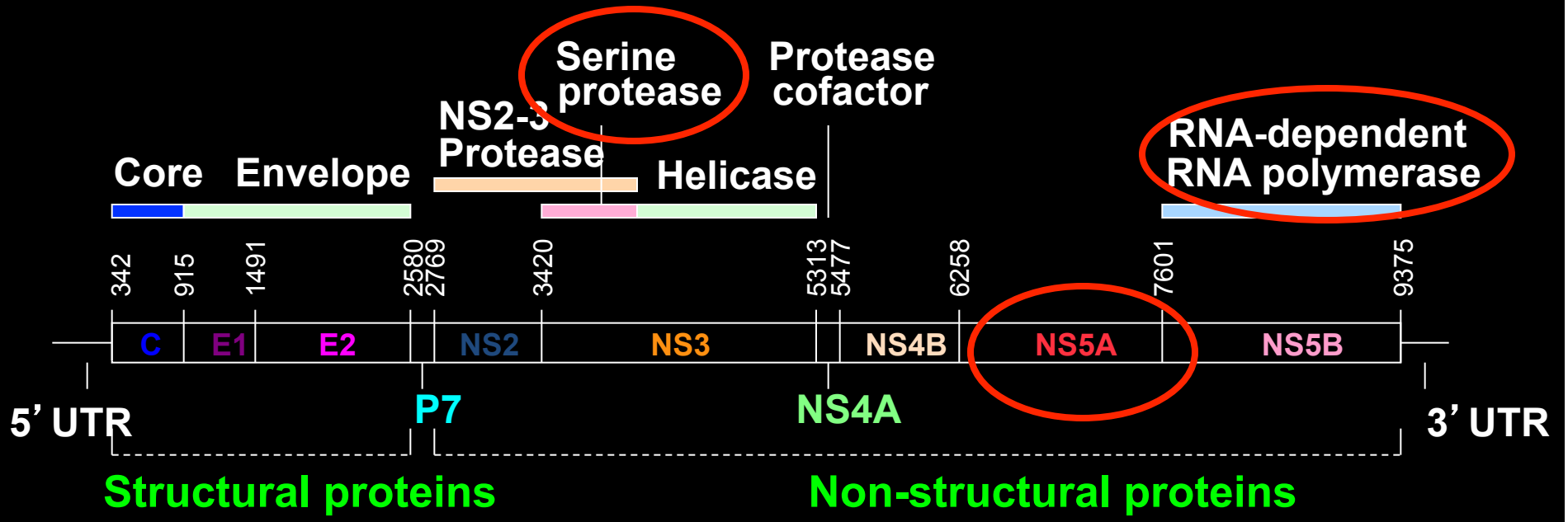
- Estimated 170-200 million person with chronic infection
- A major cause of chronic liver disease, cirrhosis, end-stage liver disease and hepatocellular carcinoma
- Leading indication for adult liver transplants in the U.S. ~50%
- Death from HCV now exceeds that of HIV
- No vaccine or specific prevention available
- Therapy is problematic and effective only in a proportion of patients

Hepatitis C Virus: Global Distribution of Infection

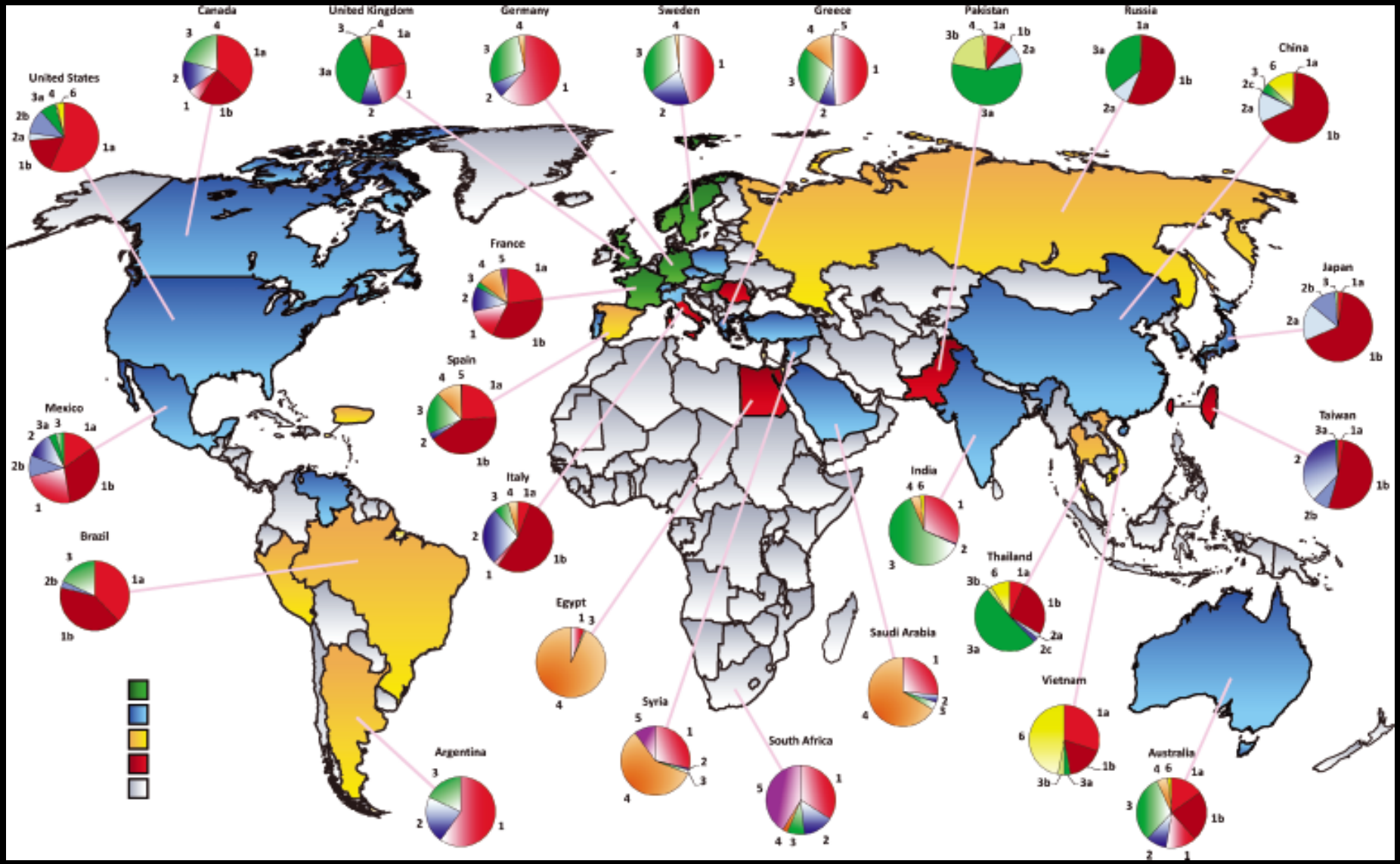


World Health Organization 2008. Available at: http://www.who.int/ith/es/index.html.

Hepatitis C Virus: Genome Organization

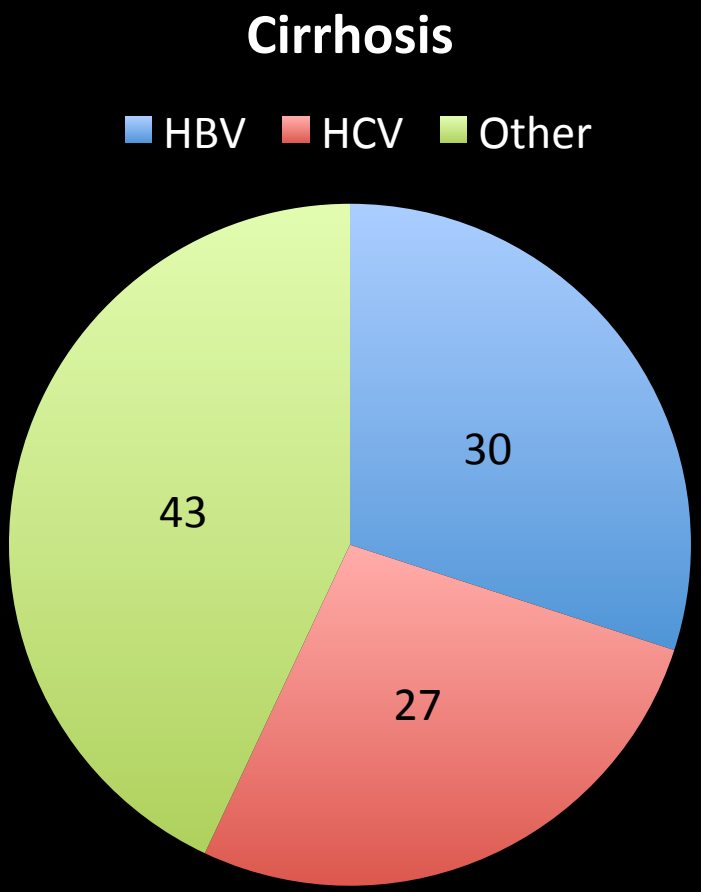


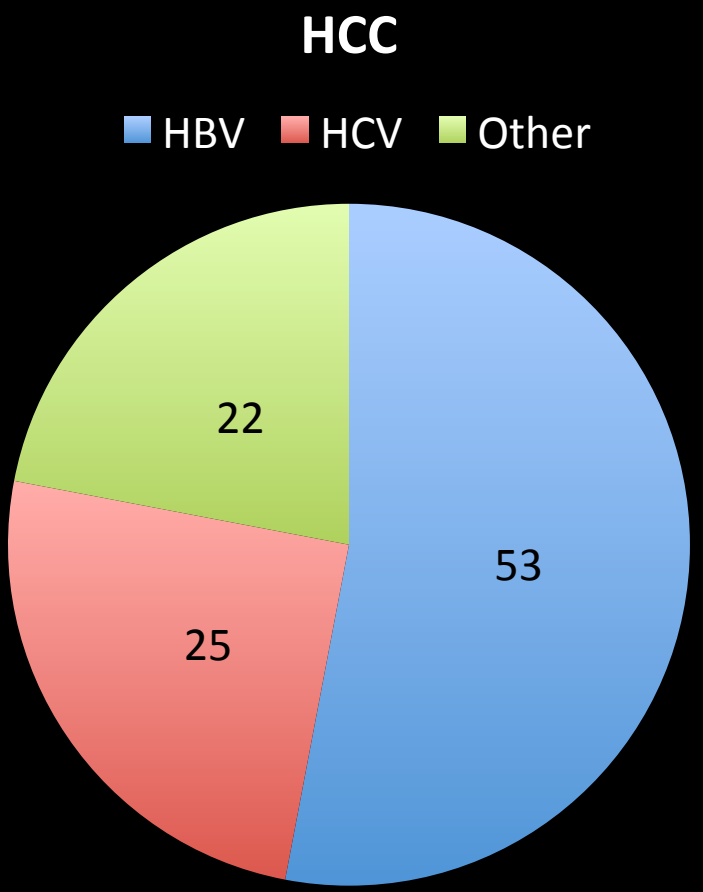
Global Distribution of HCV Genotypes



Negro F et. al. Liver Int:2011; S2:1-3

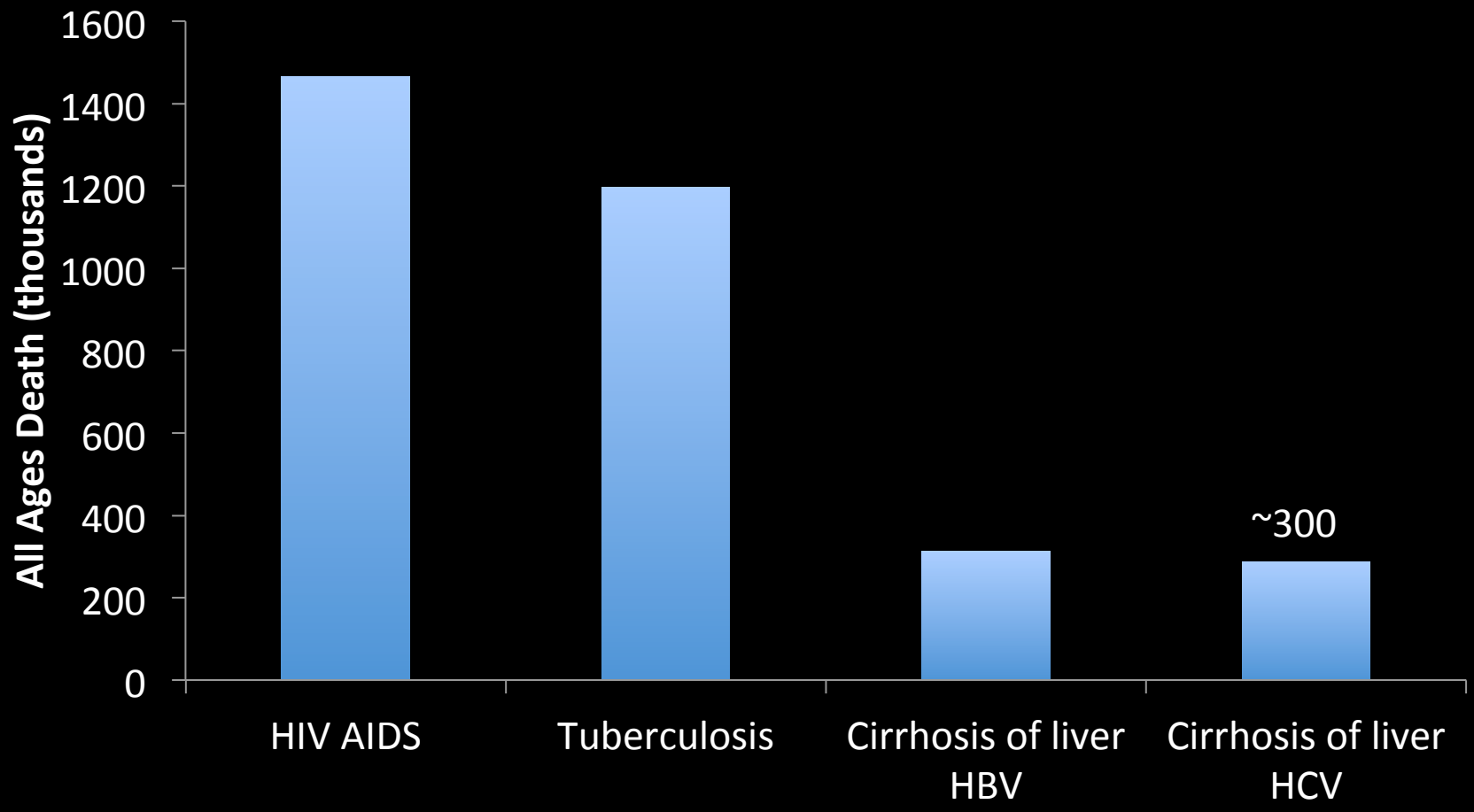
Attributable Fraction of Cirrhosis And HCC Due To HCV Infection





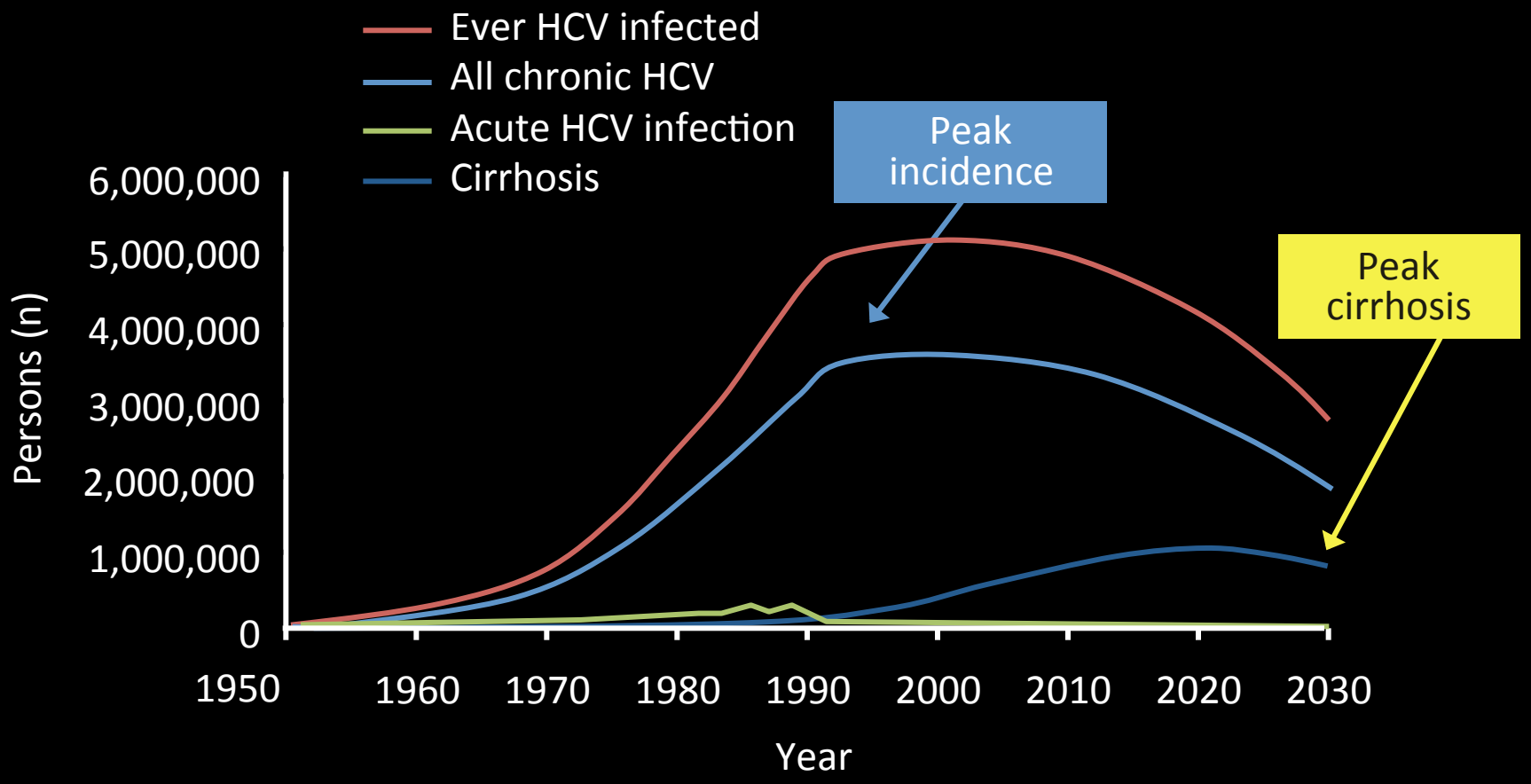
Perz JF et. Al J Hepatol 2006; 45:529-538

Global Mortality of HCV



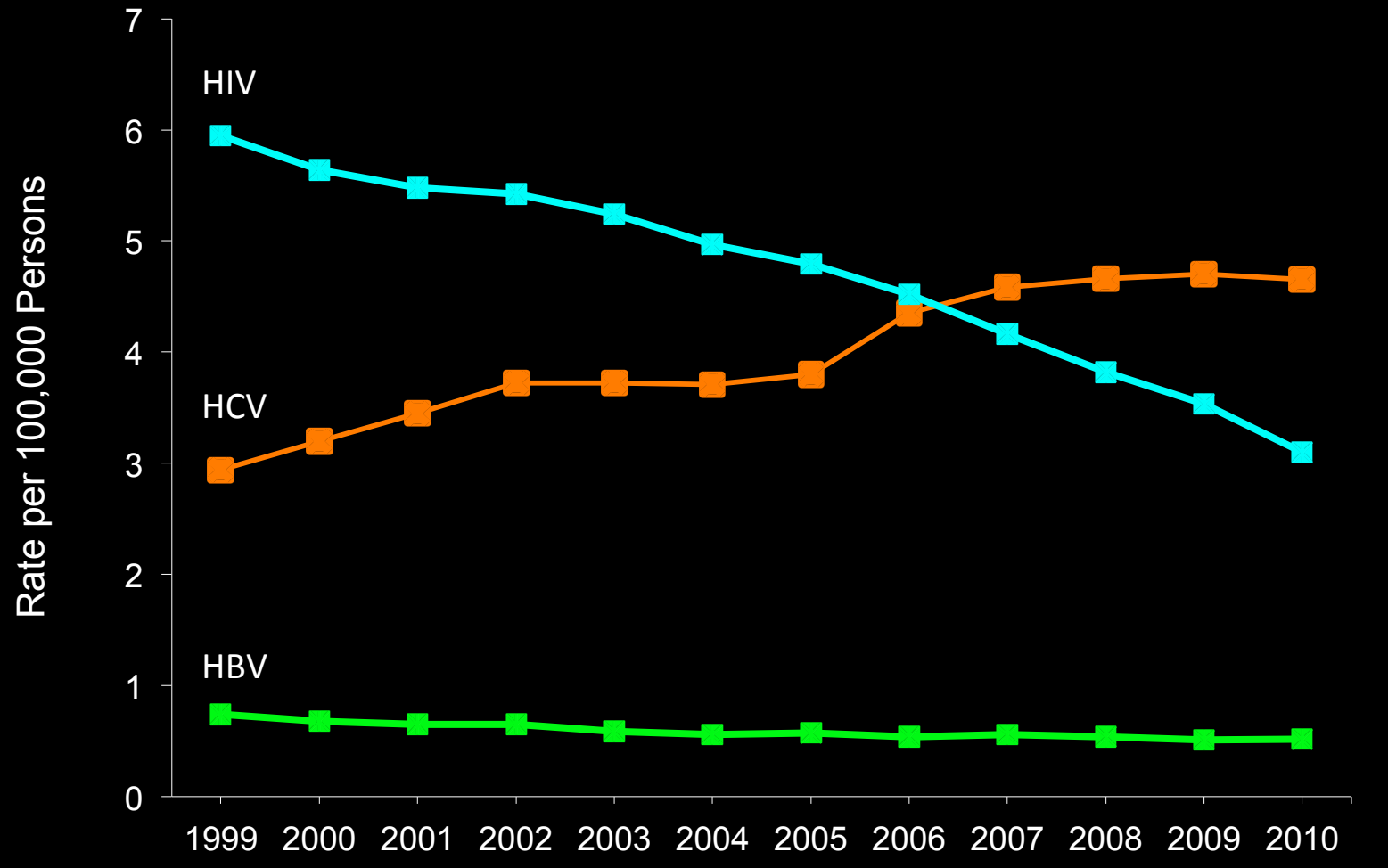
Lancet 2012;380:2095-128

The Changing Face of HCV in the US



Davis GL, et al, Gastroenterology 2010

Annual age-adjusted mortality rates from HBV and HCV and HIV infections in the United States between 1999 and 2010

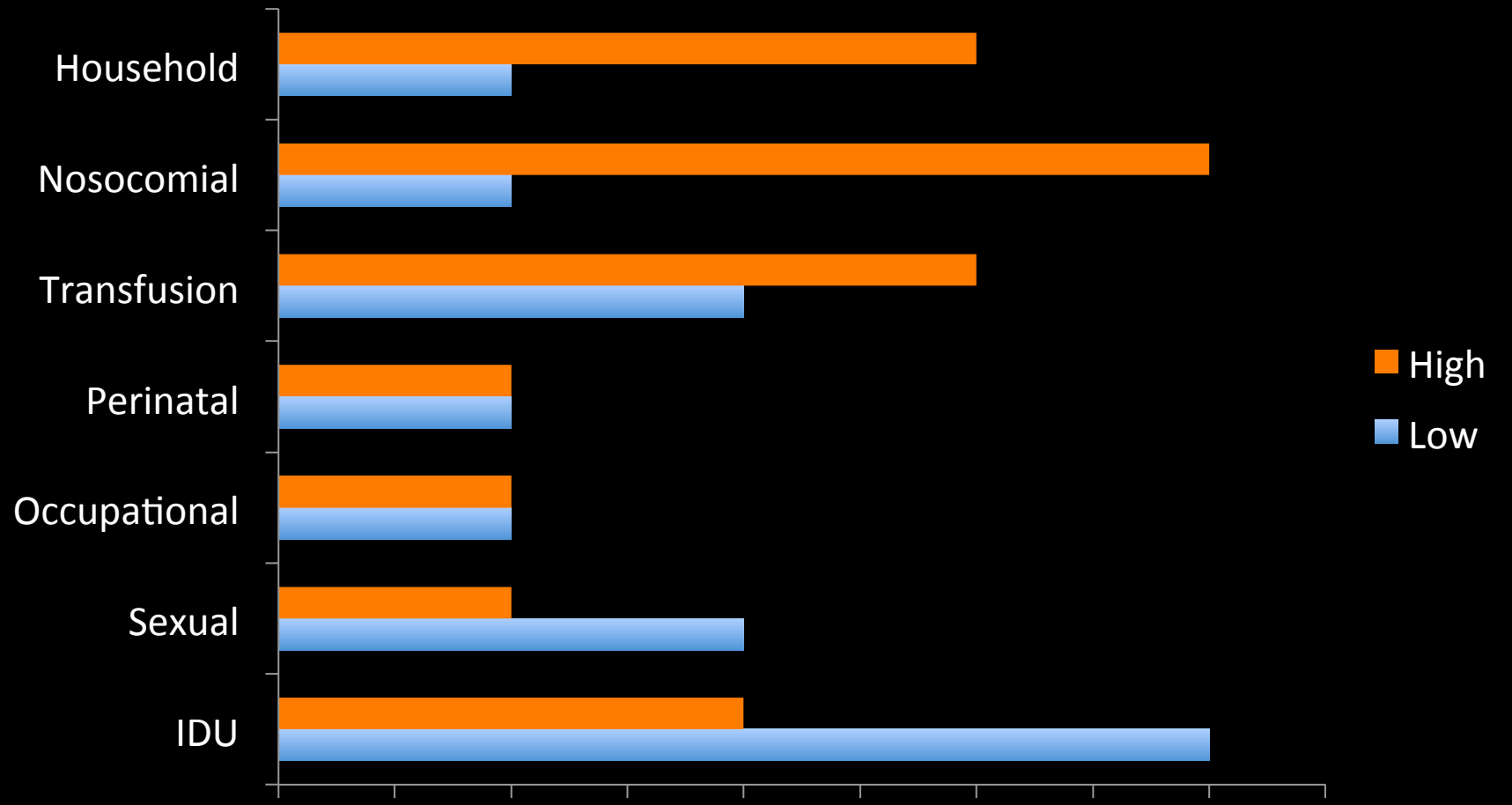


Ly, KN et al Ann Intern Med; 156:271-8

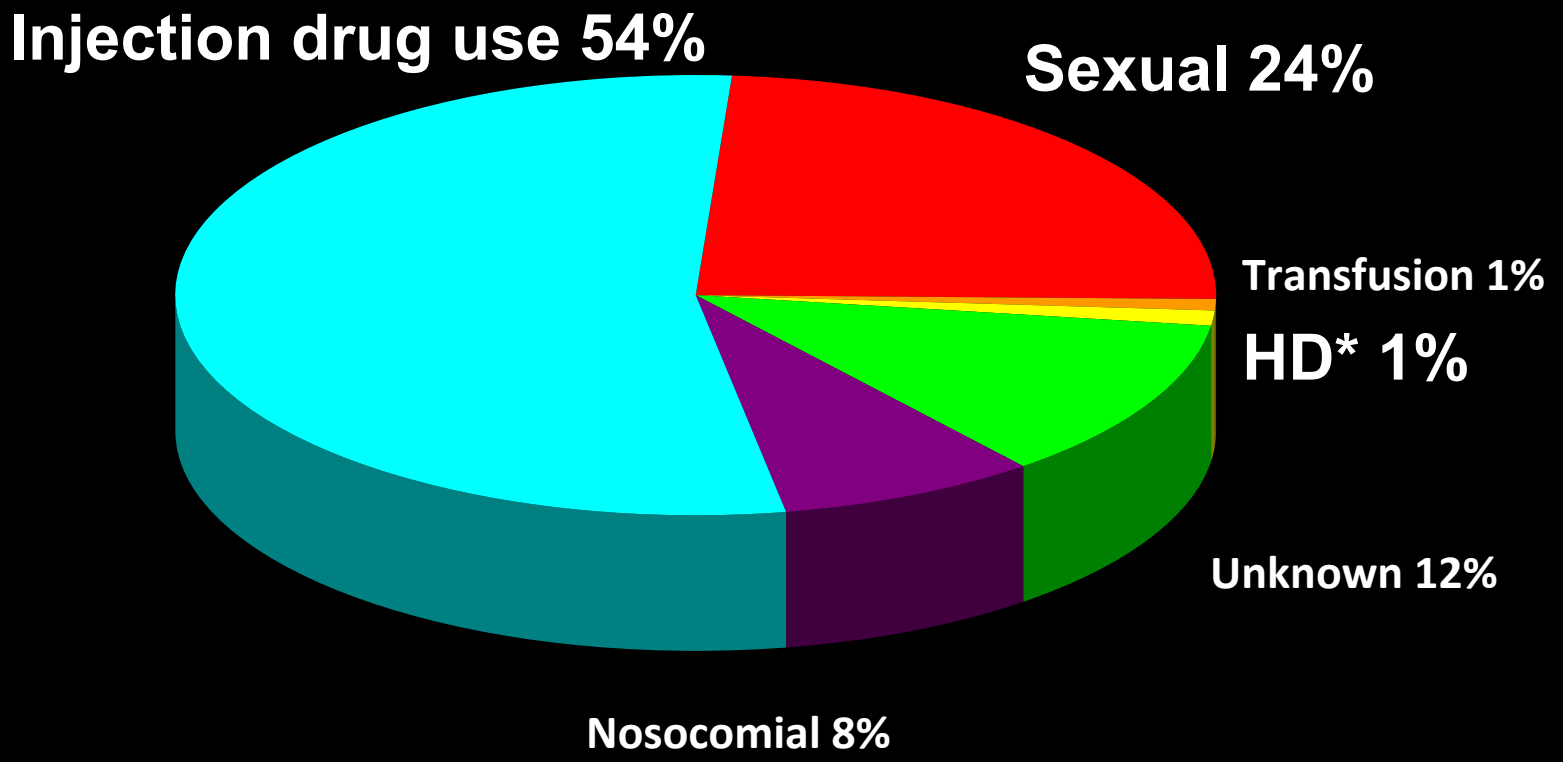
Sources of Infection: Globally

- Blood transfusions from unscreened donors
- Injection drug use
- Unsafe therapeutic injections
- Other healthcare-related procedures

Routes of Transmission Vary Depending on Prevalence of Infection



Sources of Infection in Persons with Acute Hepatitis C in the U.S.

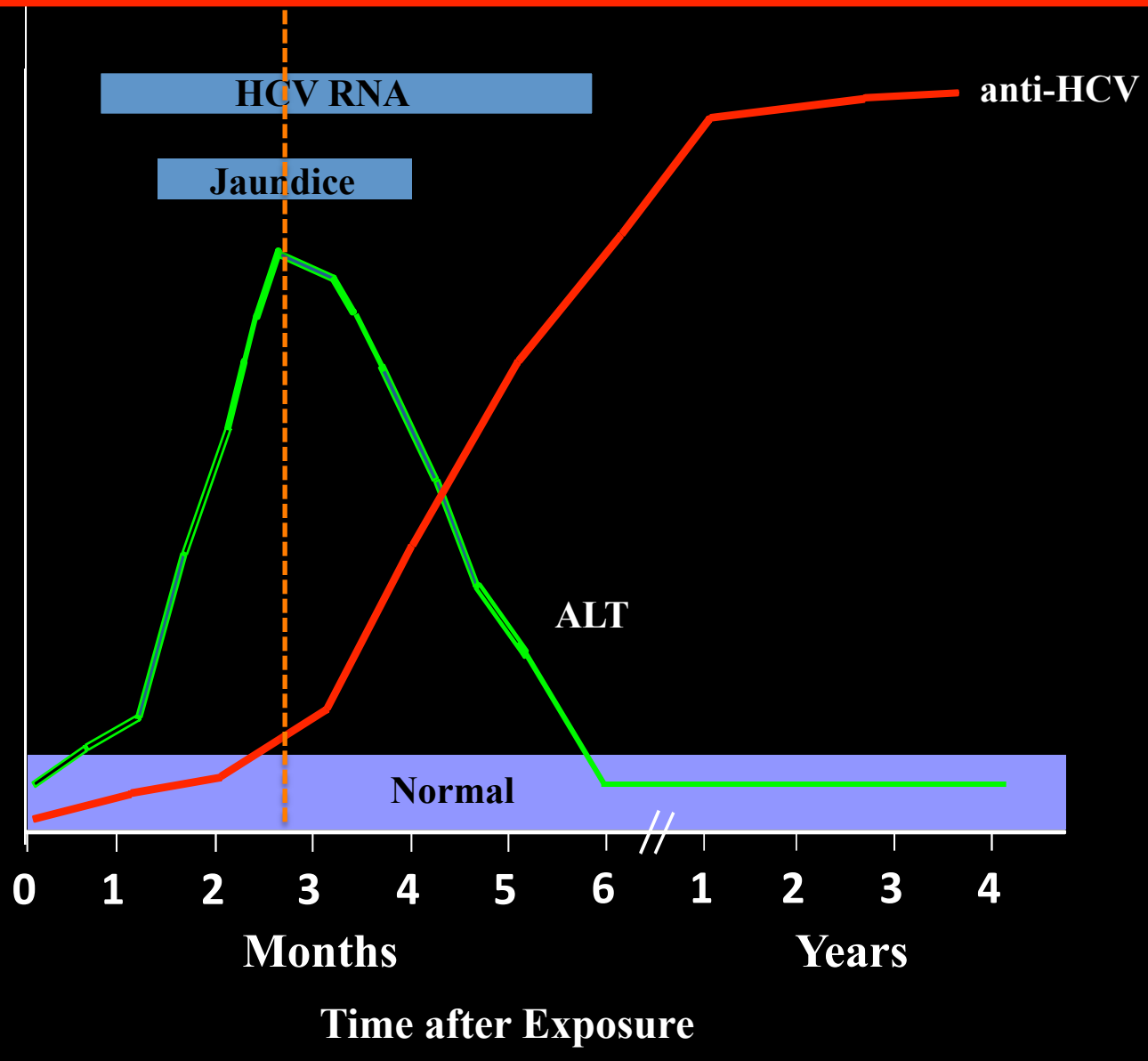


Source: MMWR April 2007

Hepatitis C: Clinical Features

- Incubation period averages 8 weeks (range, 2-26 weeks)
- Clinical manifestations include malaise, anorexia, nausea, and abdominal discomfort, followed within a few days by jaundice.

Hepatitis C: Clinical Course



Hepatitis C: 3 Clinical Patterns

- Asymptomatic (majority of cases)
- Symptomatic with jaundice (~20% of cases)
- Fulminant hepatitis (1-3% of cases)

Hepatitis C: Extrahepatic Manifestations

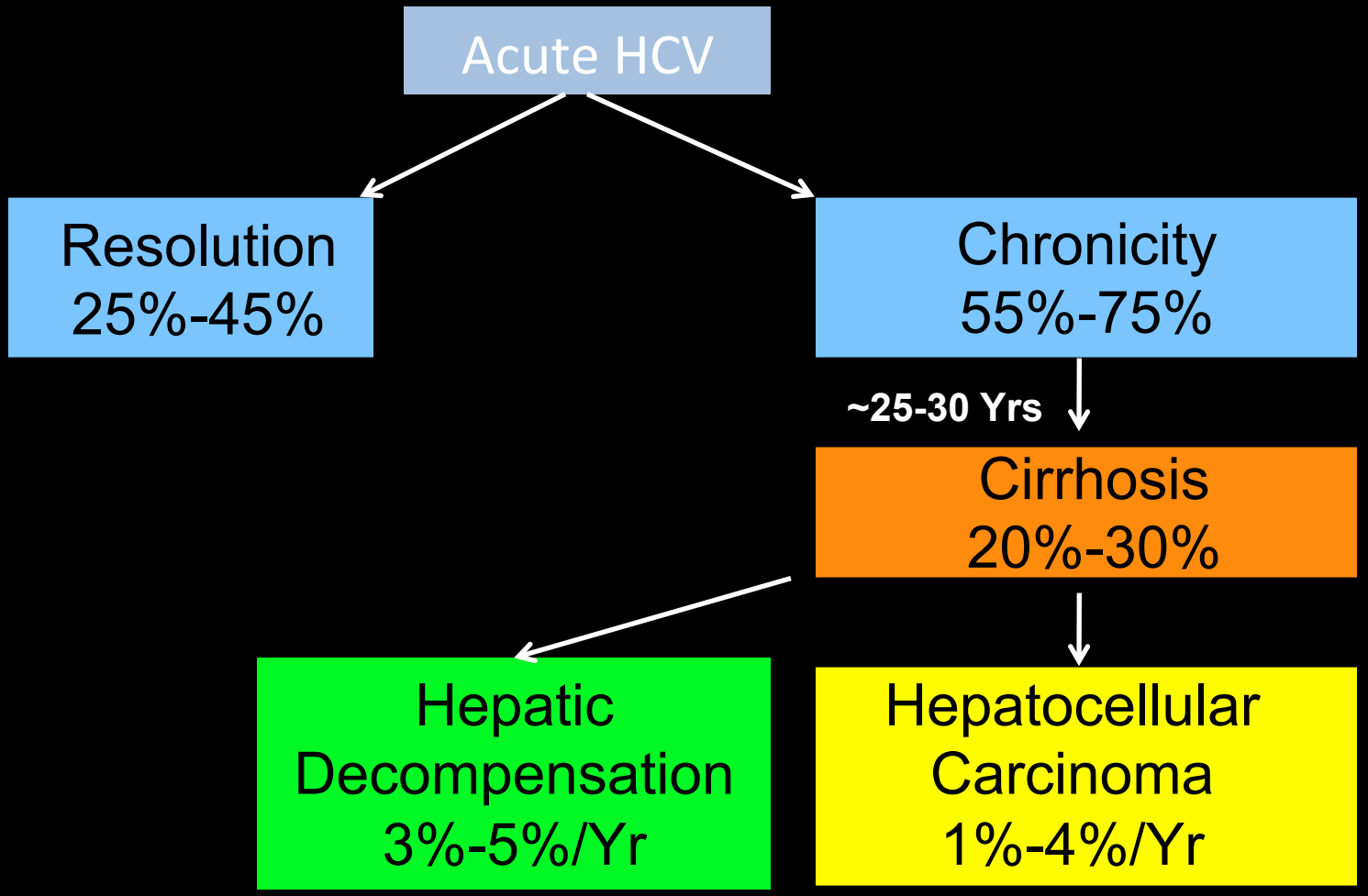
Immune-complex-mediated

- Essential mixed cryoglobulinemia
- Membrano-proliferative glomerulonephritis
- B-cell lymphoma
- MGUS

Non-Immune-complex-mediated

- Sjogren's
- Lichen planus
- Porphyria cutanea tarda
- Diabetes

Natural History of HCV Infection

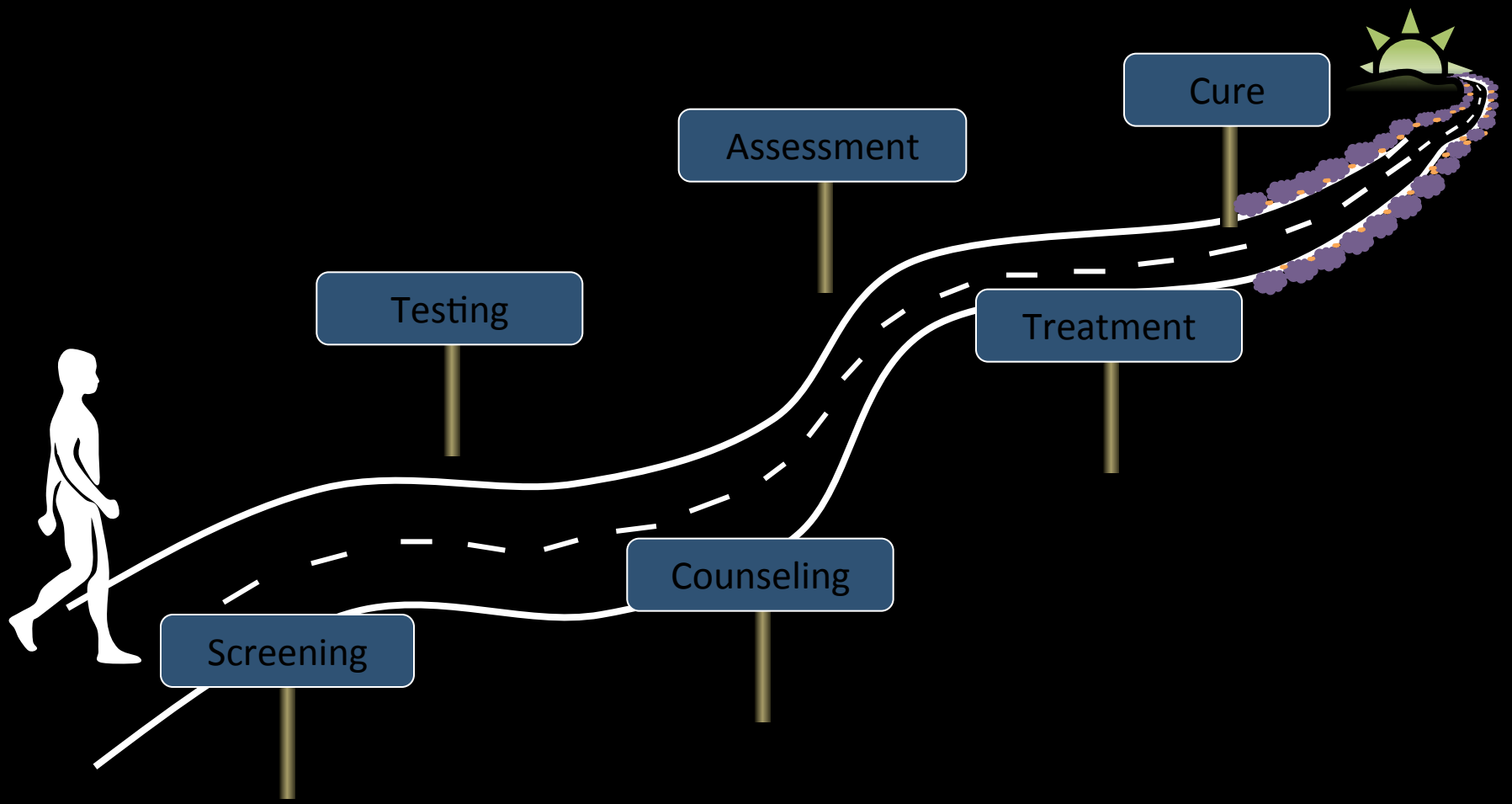


Factors Affecting Outcome of Chronic Hepatitis C

- Older age at infection
- Longer duration of infection
- Male gender (worse for male)
- Alcohol use
- Obesity
- Diabetes / insulin resistance
- Steatosis /steatohepatitis
- Co-infection with HIV or HBV
- IL28B Genotype CC
- Higher ALT elevation

Screening

HCV Screening Is the First Step on the Road to a Cure



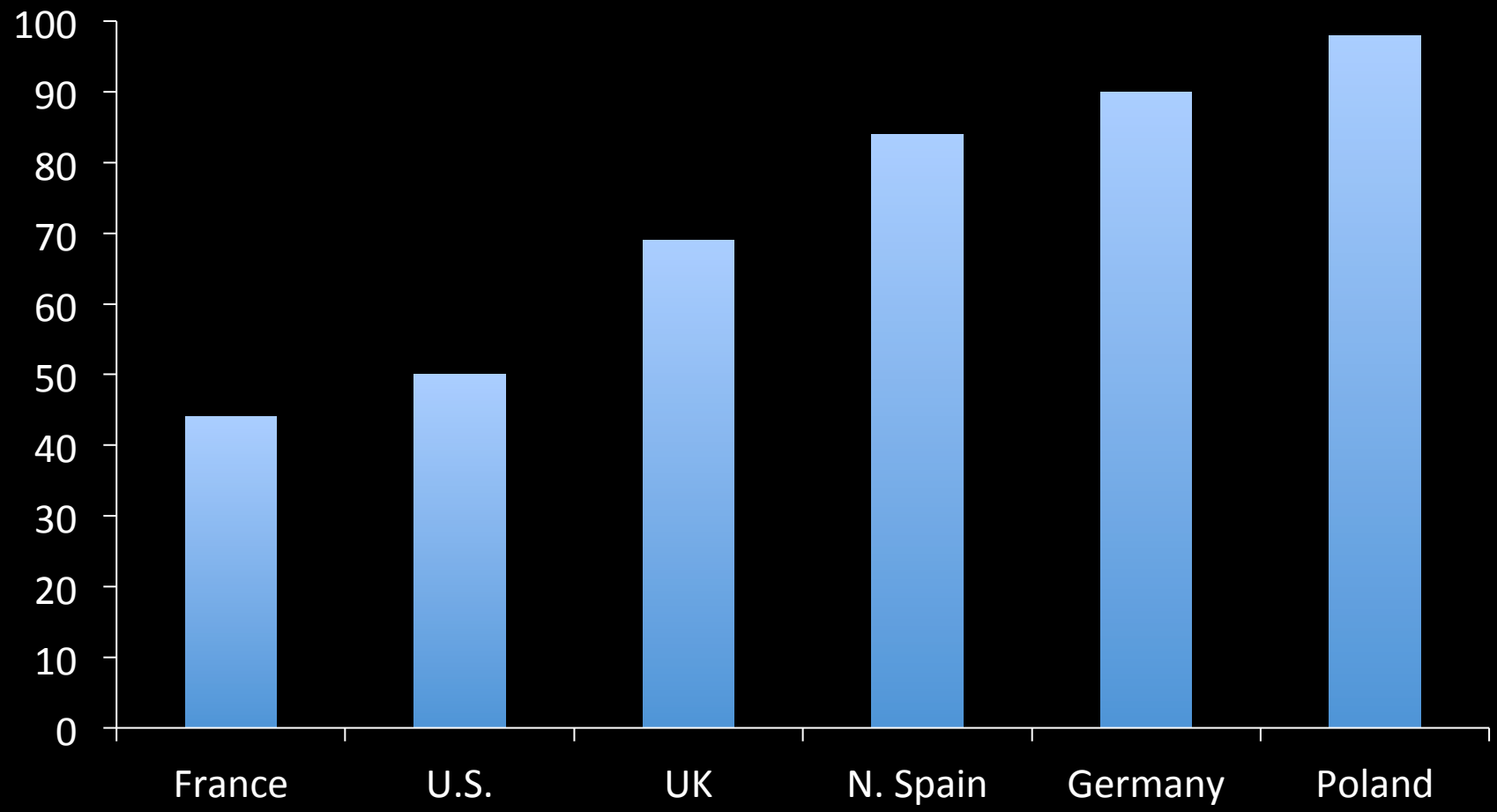
Who Should Be Screened

- Persons who have injected illicit drugs in the recent and remote past including those who injected only once and do not consider themselves to be drug users
- Persons with conditions associated with a high prevalence of HCV infection including:
  - Persons with HIV
  - Persons with hemophilia who received clotting factor concentrates prior to 1987
  - Persons who have ever been on hemodialysis
  - Persons with unexplained abnormal aminotransferase levels
- Prior recipients of transfusions or organ transplants prior to July 1992 including:
  - Persons who were notified that they had received blood from a donor who later tested positive for HCV infection
  - Persons who received a transfusion of blood or blood products
  - Persons who received an organ transplant
- Children born to HCV-infected mothers
- Health care, emergency medical and public safety workers after a needle stick injury or mucosal exposure to HCV blood
- Current sexual partners of HCV-infected persons
- Adults born between 1945-1965

Screening Criteria for HCV in The General Population

Screening Criteria	Participants with Criteria	
Persons age 20-50	General population	HCV RNA positive population
Risk factor history		
IDU	1.9	46.6
IDU or transfusion before 1992	7.3	53.1
IDU or transfusion before 1992 or >20 lifetime sex partners	21	76.1
Any illicit drug use or transfusion before 1992 or >20 lifetime sex partners	33.2	89.7
Risk Factor history and ALT Level		
Abnormal ALT level	12	62.6
Abnormal ALT level or IDU	13.3	82.8
Abnormal ALT level or IDU or transfusion before 1992	18.1	85.1
Abnormal ALT level or IDU or transfusion before 1992 or >20 lifetime sex partners	30	93.5
Abnormal ALT level or IDU or transfusion before 1992 or >20 lifetime sex partners	40.7	98.6
Persons Age >60 years		
Risk factor history		
Transfusion before 1992	17.2	60.1
Risk factor history and ALT level		
Abnormal ALT level	5.1	56.7
Abnormal ALT level or transfusion before 1992	21.1	87.4

Proportion of Subjects With CHC Who Remain Undiagnosed



Birth Cohort Screening

Rationale:

- Limited effectiveness of risk-based screening
- HCV morbidity and mortality is increasing
- Treatment is improving

Recommendation by CDC:

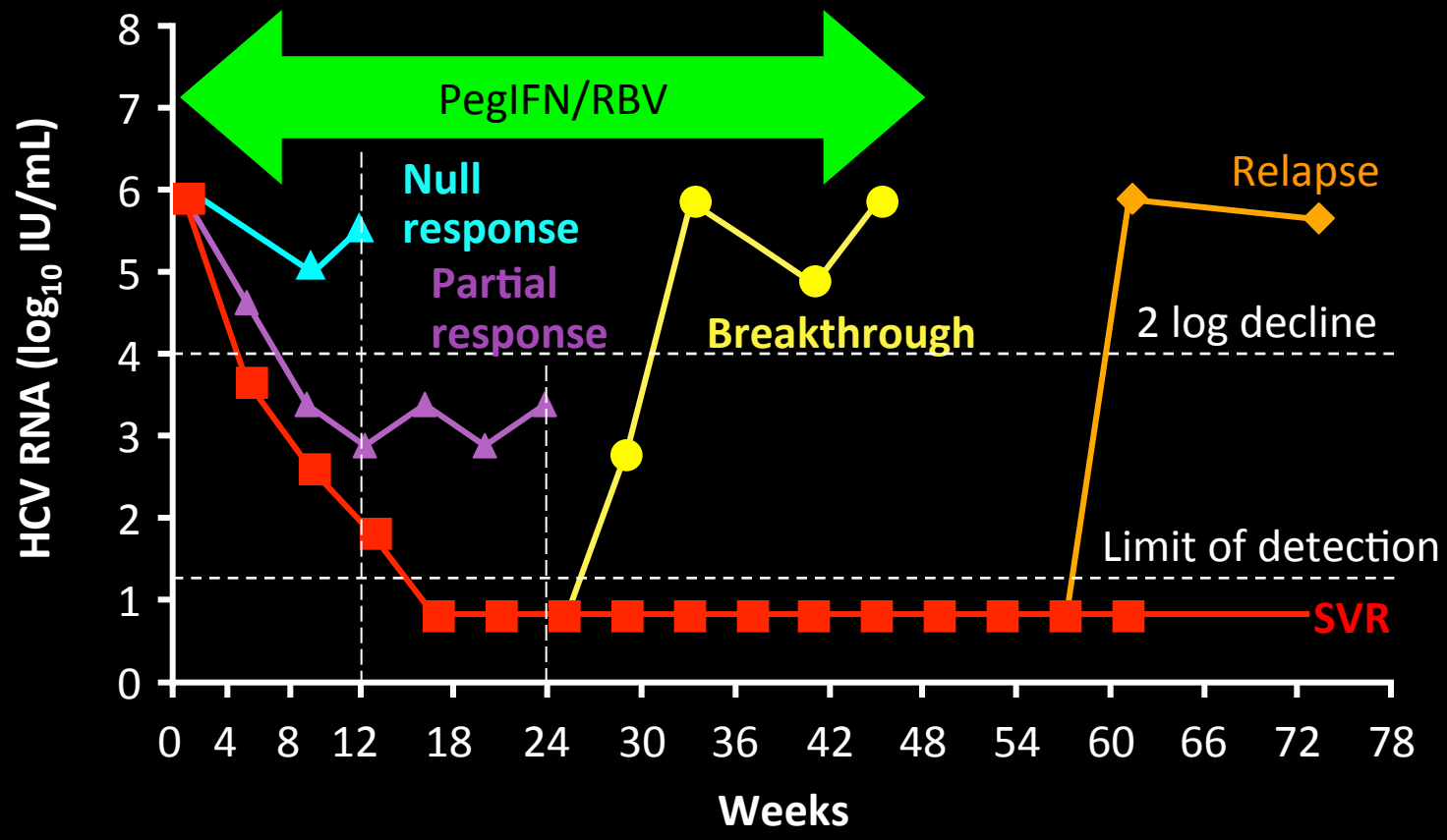
- Screen all persons born between 1945-1965
  - Prevalence of anti-HCV 3.25%
  - Accounts for >three fourths of total anti-HCV prevalence in the U.S.

MMWR 2012:61:No 4

Hepatitis C: Goals of Therapy

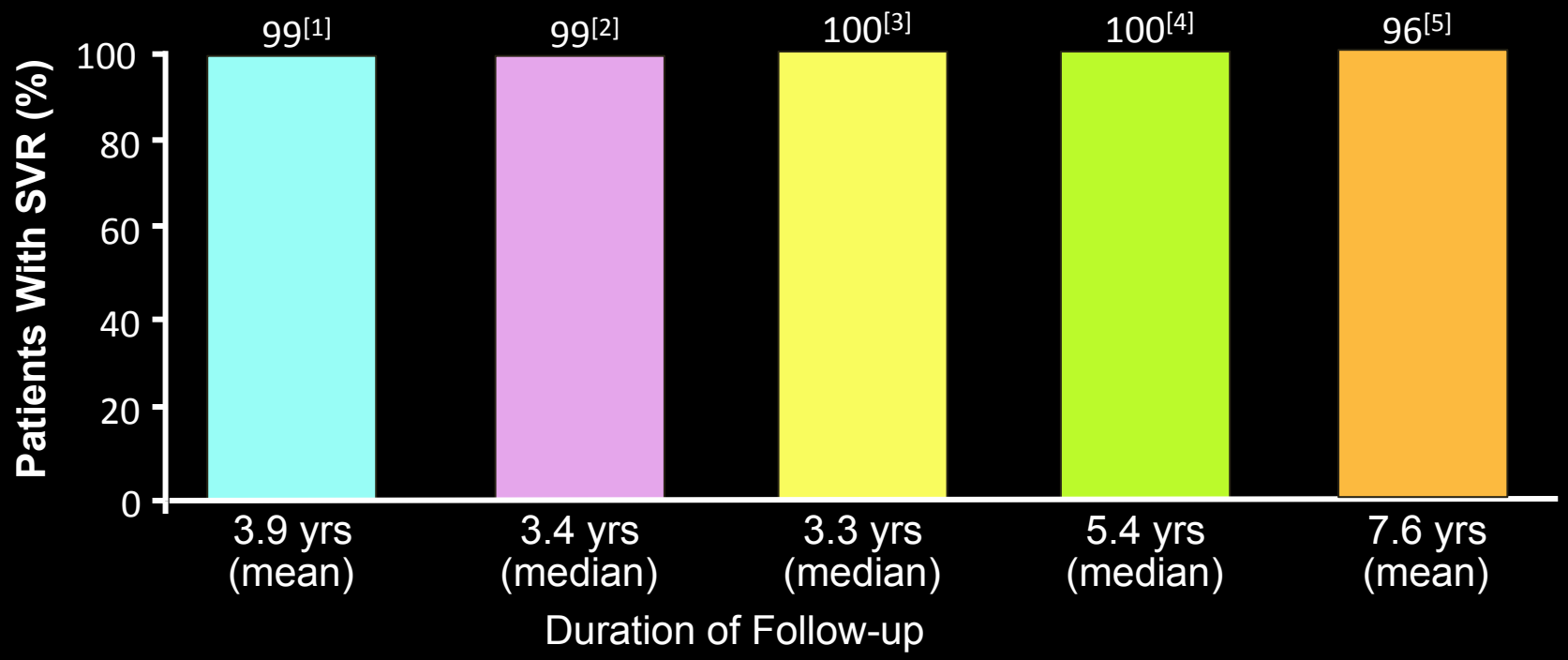
- *Prevent the development of complications:*
  - Cirrhosis
  - End-stage liver disease
  - Hepatocellular carcinoma
  - Liver-related death
- Surrogate endpoint is the sustained virological response 12 weeks after stopping therapy SVR_{12}

Outcomes of Therapy for CHC



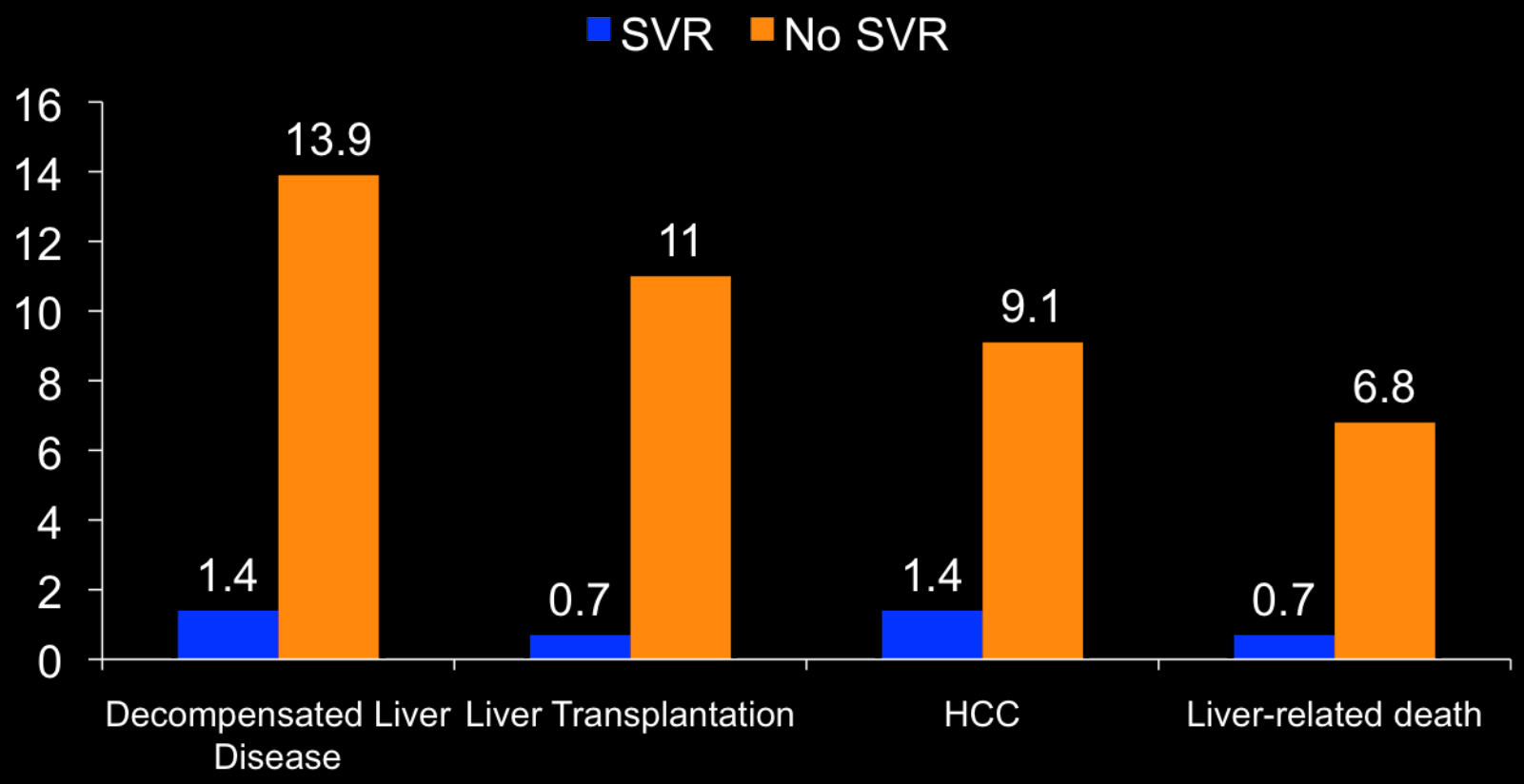
SVR Equivalent to Virological Cure

- Nearly 100% of patients who achieve SVR remain undetectable during long-term follow-up[1-4]



[1]Swain MG, et al. Gastroenterology. 2010;139:1593-1601. [2]Giannini EG, et al. Aliment Pharmacol Ther. 2010;31:502-508. [3]Maylin S, et al. Gastroenterology. 2008;135:821-829. [4]George SL, et al. Hepatology. 2009;49:729-738.[5] Koh C et al Hepatology 2010

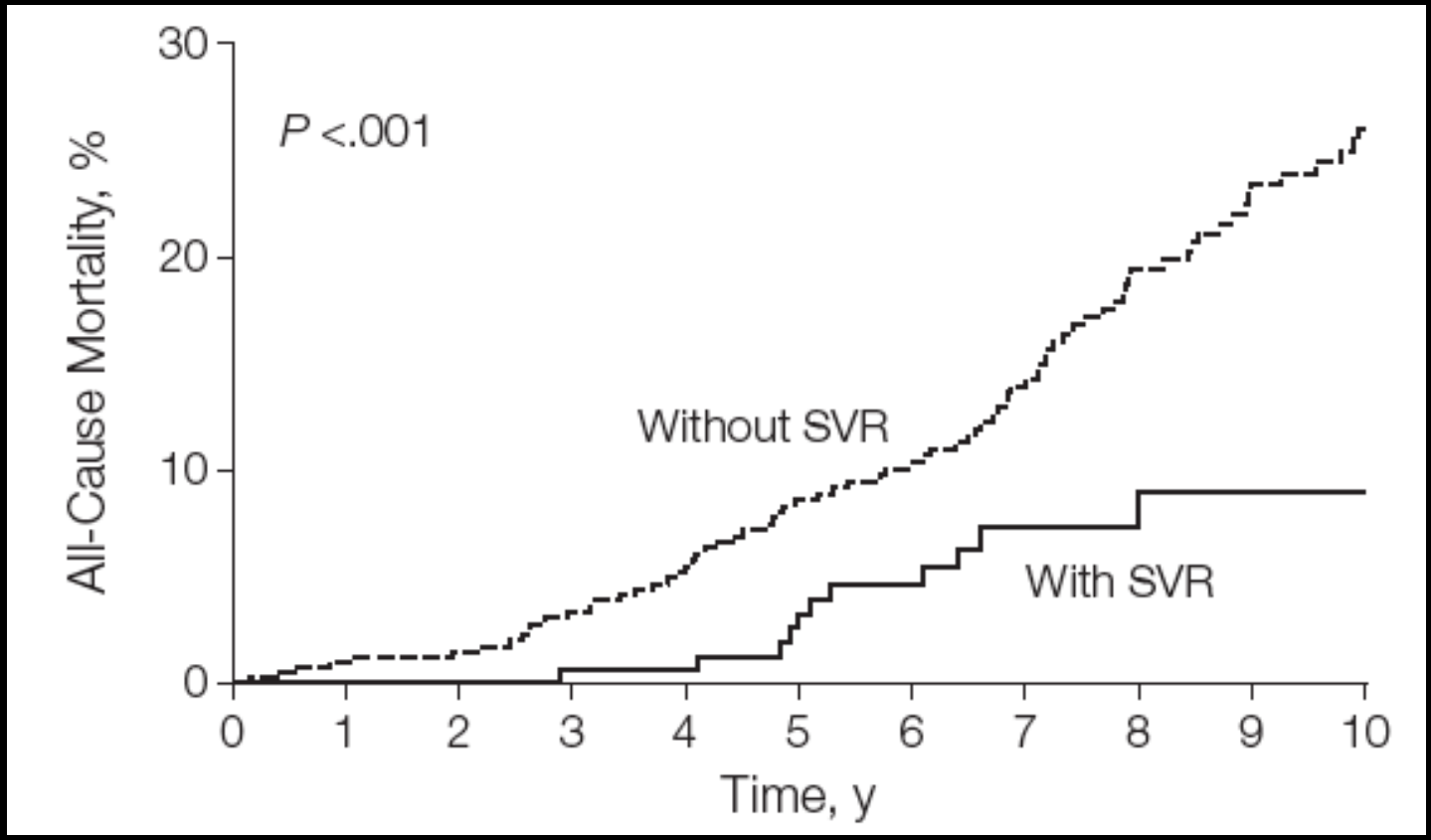
SVR Associated with Improved Outcomes in Patients with HCV and Advanced Fibrosis



Morgan et al. Hepatology 2010;52: 833

SVR Is Associated With Improved Survival

530 patients with chronic HCV infection with advanced fibrosis or cirrhosis (Ishak 4-5) who received an interferon-based treatment regimen between 1990 and 2003, followed for a median of 8.4 years for all cause mortality and liver-related mortality.



Van der Meer et al JAMA 2012;308:2584-93

Optimal Therapy of Hepatitis C Genotype 1: 2014

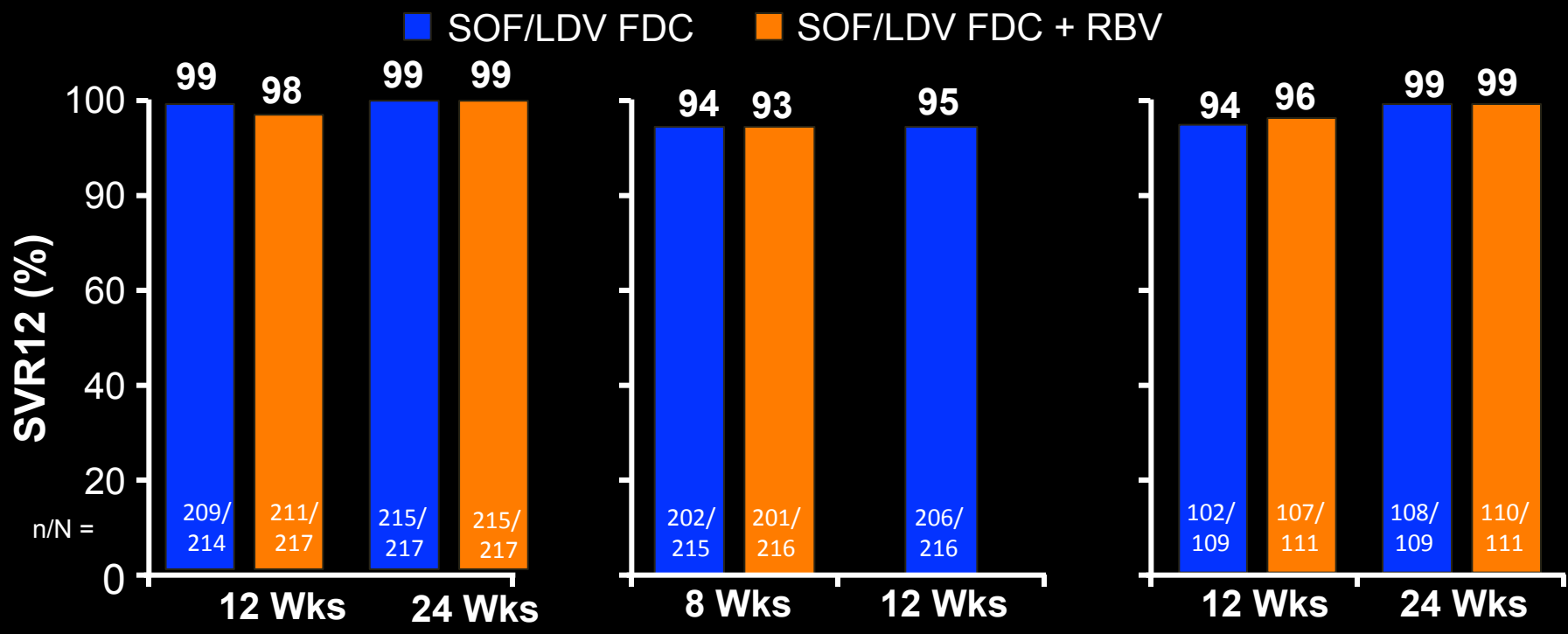
- Peginterferon (by injection)
  - alfa-2a 180 μg weekly
  - alfa-2b 1.5 μg/kg weekly
- Ribavirin (by mouth)
  - 1,000-1,200 mg in two divided doses daily

Combined with either:

- Sofosbuvir (Nucleoside analogue) (by mouth)
  - 400 mg once per day
  - For 12 weeks
- Simeprevir (Protease inhibitor) (by mouth)
  - 150 mg once per day
  - For 12 weeks (total duration 24 weeks)

Sofosbuvir & Ledipasvir ± RBV in Treatment-Naïve or -Experienced GT1 HCV

ION-1*: GT1 treatment-naive pts (16% cirrhotic): SOF/LDV FDC ± RBV for 12 wks	ION-3: GT1 treatment-naive pts: SOF/LDV FDC ± RBV for 8 or 12 wks	ION-2: GT1 treatment-experienced pts (20% cirrhotic): SOF/LDV FDC ± RBV for 12 or 24 wks

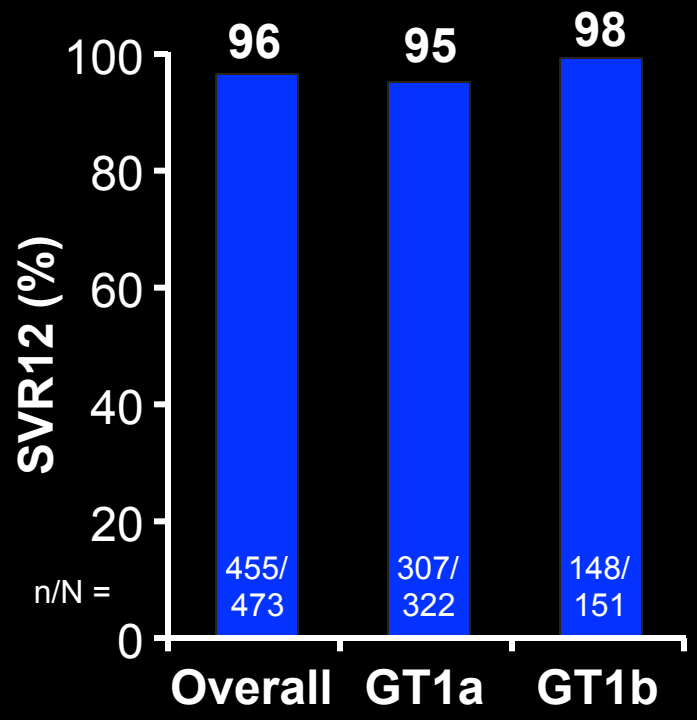


*24-wk arms not yet reported.

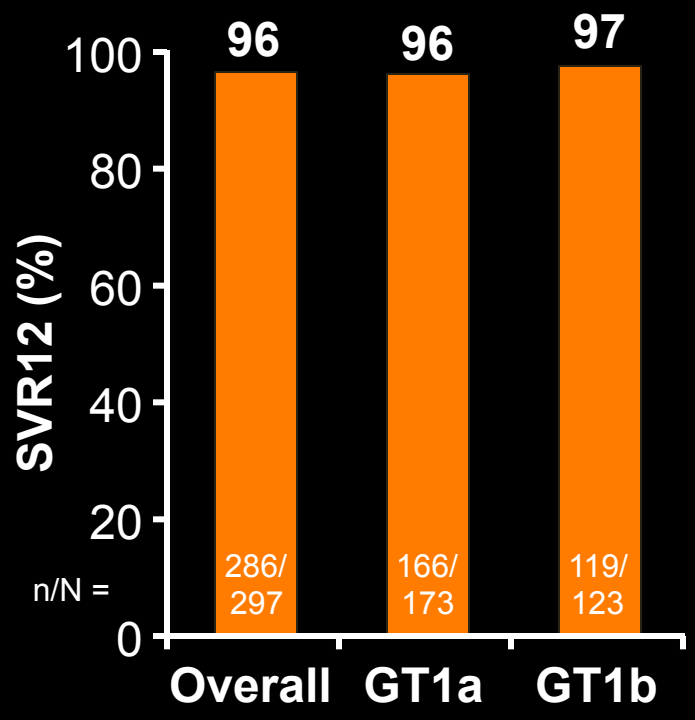
Gilead Press release Dec 18th, 2013

ABT-450/RTV & ABT-267 & ABT 333 & RBV in Treatment-Naïve or -Experienced GT 1 HCV

SAPPHIRE-1: GT1 treatment-naive noncirrhotic patients:
ABT-450/RTV/ABT-267 FDC
+ ABT-333 + RBV for 12 wks

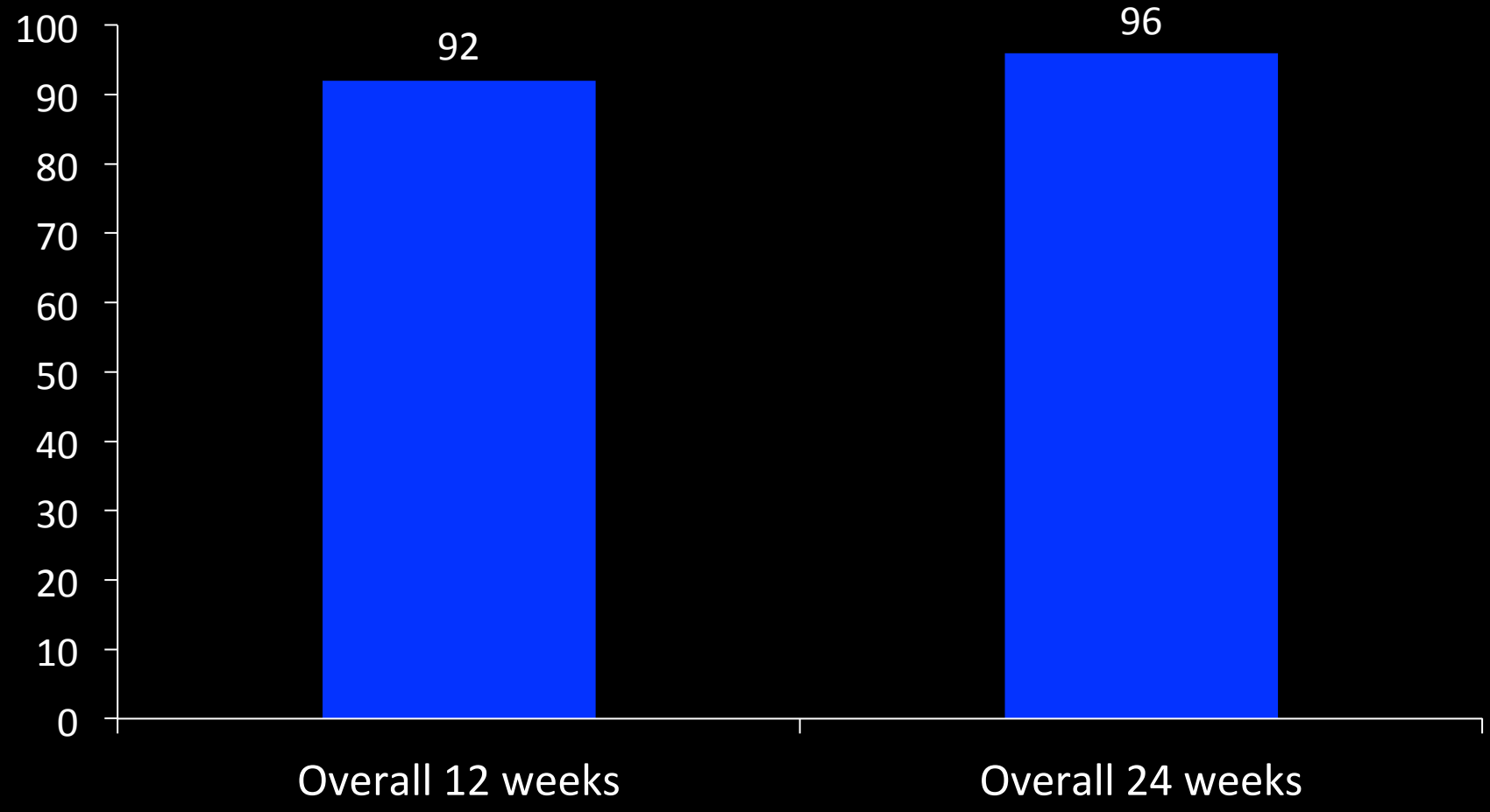


SAPPHIRE-2: GT1 treatment-experienced noncirrhotic patients (49% null responders):
ABT-450/RTV/ABT-267 FDC
+ ABT-333 + RBV for 12 wks



Abbvie Press release Nov 18th 2013; Dec 10th 2013

ABT-450/RTV & ABT-267 & ABT 333 & RBV in Treatment-Naïve or -Experienced GT 1 HCV with Cirrhosis



Abbvie Press release Nov 18th 2013; Dec 10th 2013

Optimal Therapy of Hepatitis C Genotypes 2 & 3 : 2014

Sofosbuvir (by mouth)

- 400 mg daily

Ribavirin (by mouth)

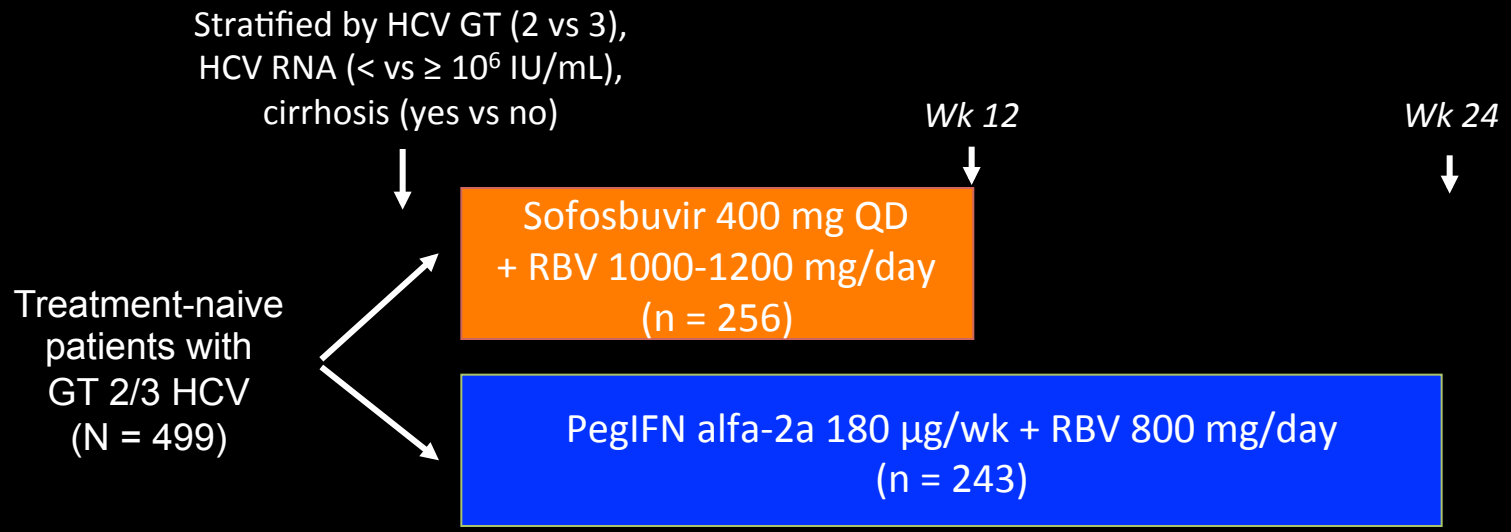
- 1,000 to 1,200 mg in two divided doses daily

For 12 weeks (Genotype 2)

For 24 weeks (Genotype 3)

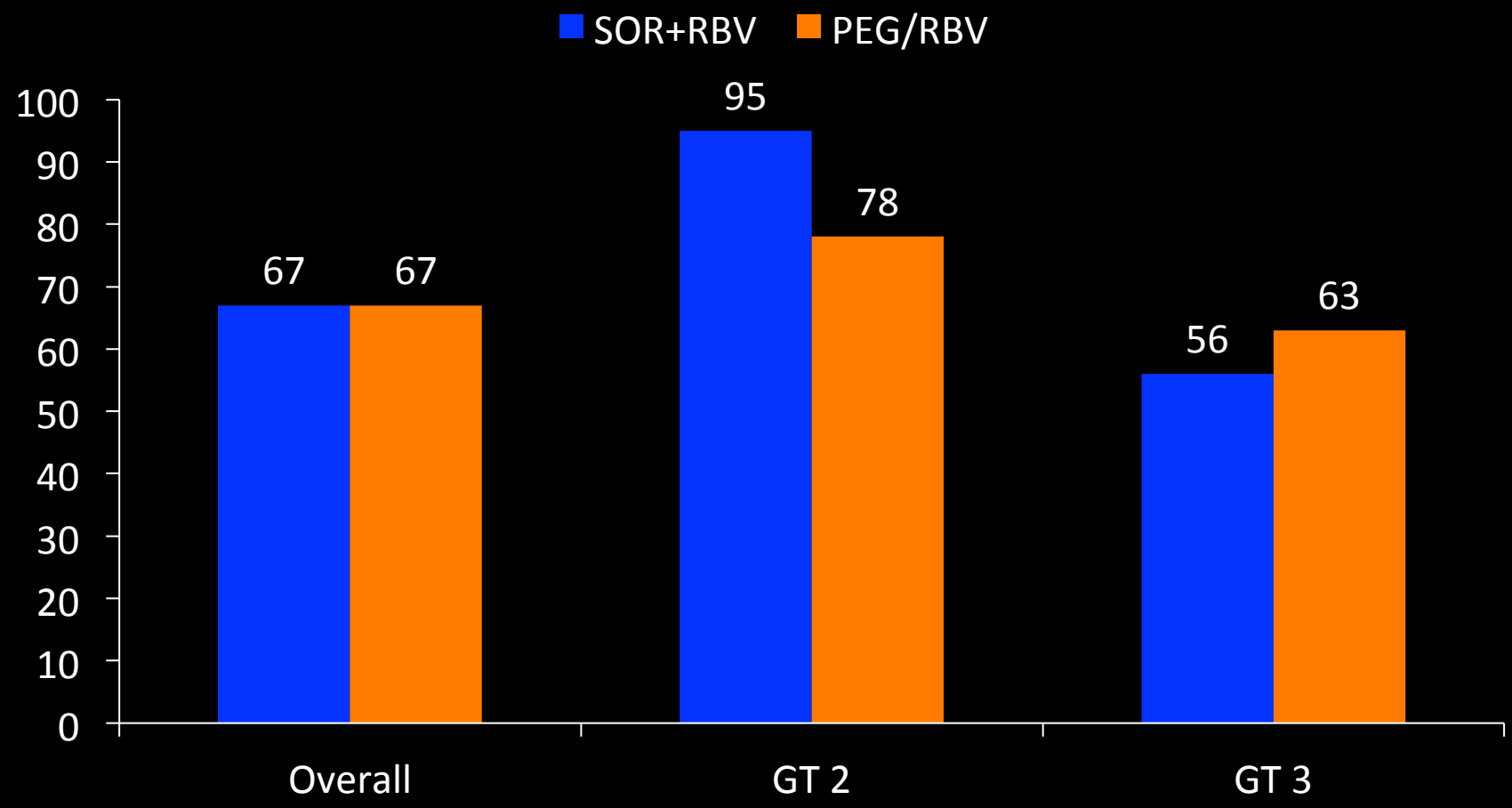
FISSION: Sofosbuvir/RBV vs PegIFN/RBV in Treatment-Naive GT 2/3 HCV Patients

- Randomized, controlled, phase III noninferiority trial
  - 20% to 21% had cirrhosis; 72% had GT 3 HCV



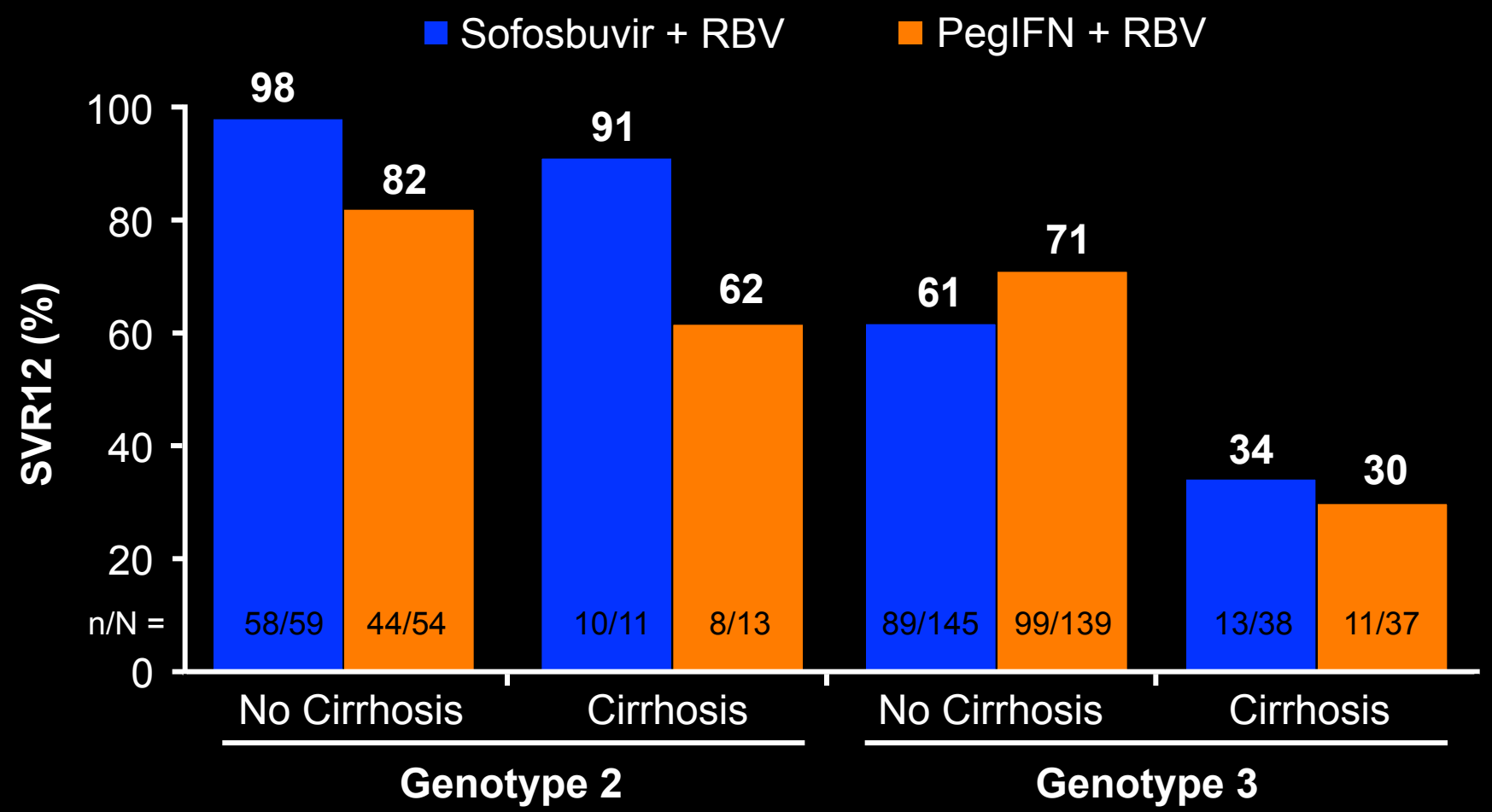
Gane E, et al. EASL 2013. Abstract 5.

FISSION: Sofosbuvir/RBV Noninferior to P/R in Tx-Naive GT 2/3 HCV Patients



Gane E, et al. EASL 2013. Abstract 5.

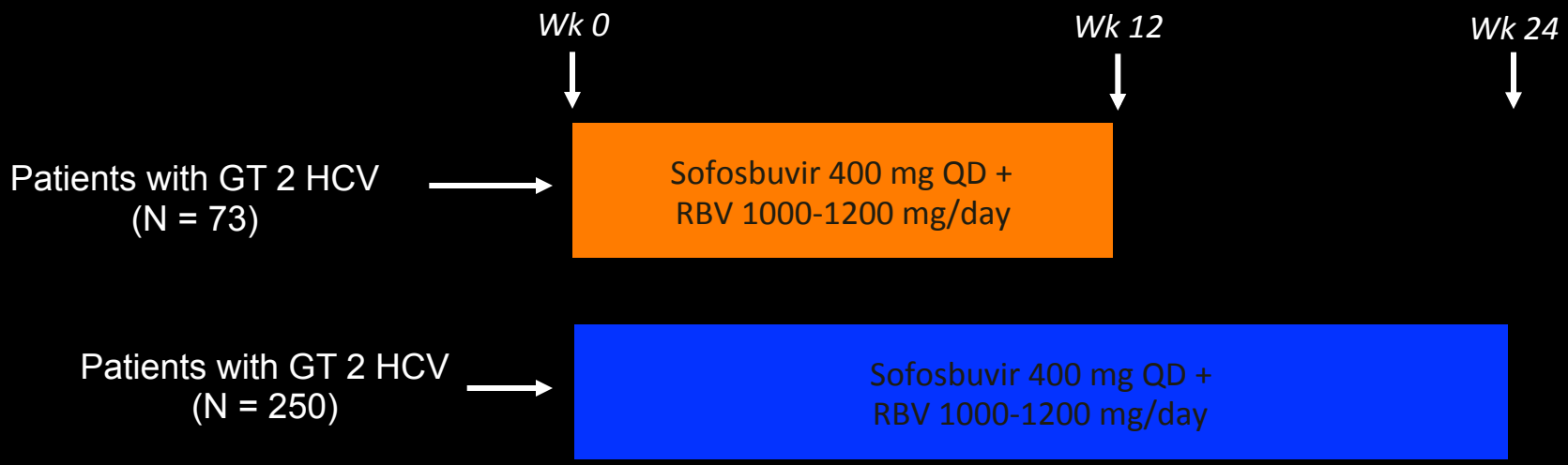
FISSION: SOF/RBV x 12 Wks: SVR12 By Genotype and Fibrosis Level



Gane E, et al. EASL 2013. Abstract 5..

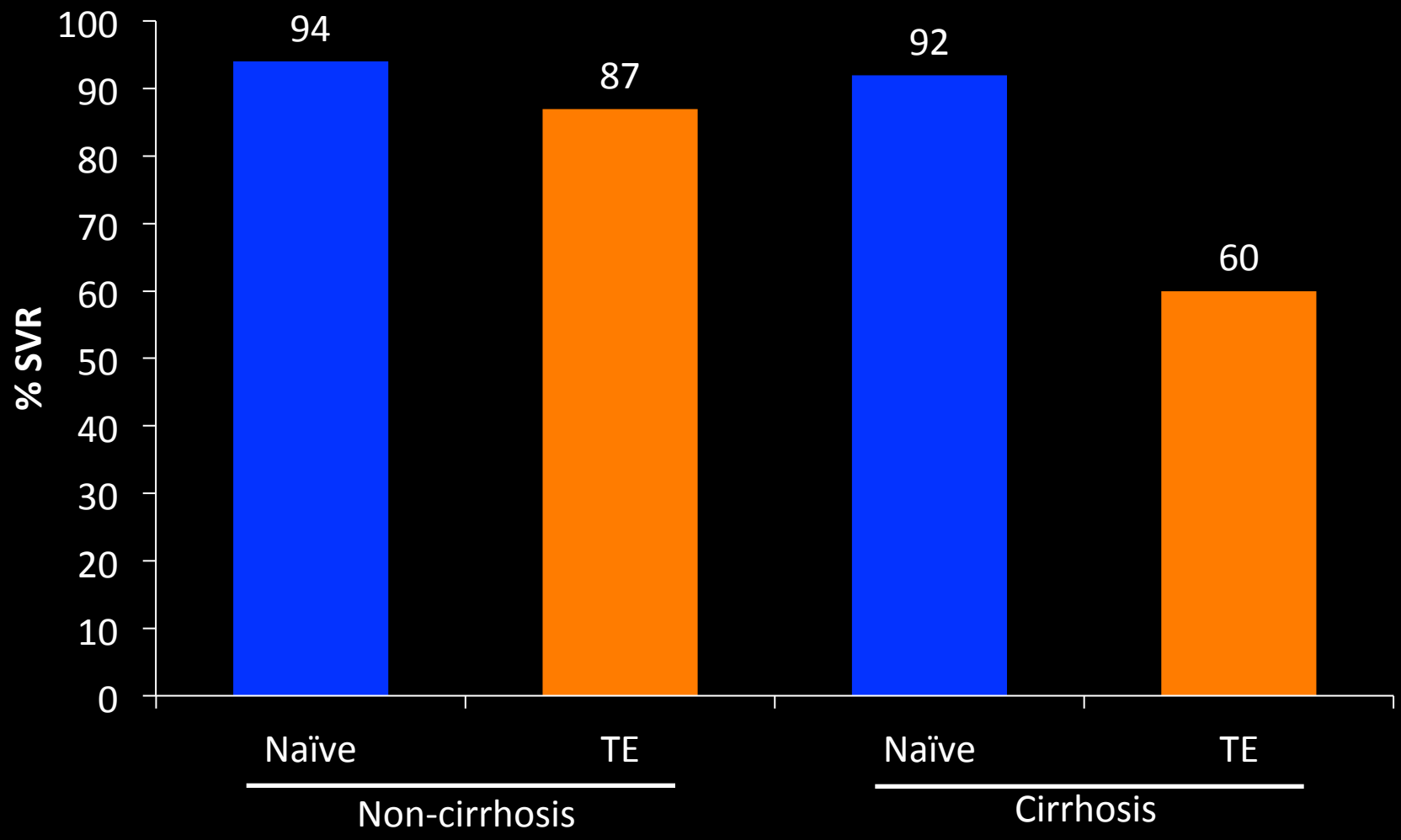
Valence: Sofosbuvir + RBV for 12 or 24 Wks in Tx-Experienced GT 2/3 HCV Patients

- Initially randomized, placebo controlled study of sofosbuvir & ribavirin for 12 weeks. Amended to open-label trial of sofosbuvir & ribavirin for 12 weeks in GT 2 and 24 weeks in GT3 patients
  - 62% to 64% had GT 3 HCV, 33% to 35% had cirrhosis, 75% to 76% were previous relapsers



Nelson D, et al. EASL 2013. Abstract 6.

Valance GT 3: SOF&RBV X 24 Weeks



Zeuzem S et al. AASLD 2013 Abstract 1085

Advantages of Future Therapies

- Once-daily dosing
- High potency
- Shorter duration of therapy
- Simpler regimens—no lead-in or response guided therapy
- Fewer adverse events
- IFN and perhaps ribavirin free regimens

Progress in Therapy of Hepatitis C